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Introduction

This chapter addresses evidence on smoking and health effects over a range of specific diseases and nonspecific but adverse consequences. The associations reviewed appear to reflect both specific and nonspecific pathways of injury by tobacco smoke. The evidence indicates that smoking should be considered not only a cause of specific diseases and conditions, but a contributing factor to nonspecific morbidity and a diminished quality of life.

Diminished Health Status

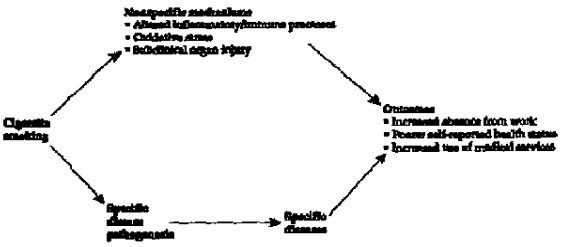
This section focuses on the question of whether cigarette smokers have poorer health in comparison with nonsmokers, beyond the already well-characterized burden of morbidity and mortality from the specific diseases caused by smoking. The hypothesis that smoking might impair health in general draws plausibility from the toxicologic richness of tobacco smoke, the well-documented systemic distribution of tobacco smoke components and metabolites, and the effects on host defenses, including the immune system. Additionally, impairment of organ function short of the level at which clinical disease is diagnosed may leave the smoker vulnerable to otherwise well-tolerated threats to health. For example, the reduction of lung function found in many smokers who do not have overt chronic obstructive pulmonary disease (COPD) may increase the risk for developing a more severe illness with a respiratory infection, or having a respiratory complication following surgery.

This section reviews studies that have addressed a number of health status indicators (Figure 6.1) including direct reports of health status or responses to an instrument that provides a health status index, and indirect indicators such as medical services utilization data. When interpreting the findings of these studies, consideration needs to be given to the potential causal pathways linking smoking to a poor health status, the assessment and measurement of health status, and the potential for biases, such as from confounding, to affect associations of smoking with these outcome measures.

For the diseases caused by smoking, direct causal pathways are implicit. For example, substantial evidence supports the hypothesis that smoking causes lung cancer through the direct deposition of tobacco smoke carcinogens in the respiratory tract. For some of the outcome measures considered in this section, pathways are far less certain and may be both direct and indirect. Increased absenteeism might reflect, for example, the tendency of smokers to have more severe respiratory illnesses than nonsmokers, possibly attributable to the effects of smoking on respiratory defenses or because smokers tend to have a lower level of lung function.

The outcomes considered in this section have multiple determinants. Health status itself is an integrative measure reflecting the net consequences of the many varied factors that determine health and well-being. To the extent that smokers differ from nonsmokers in these factors, there is a potential for confounding to distort associations of smoking with the outcome measures. Studies show, for example, that smokers and nonsmokers differ in aspects of lifestyle and in their approaches to health care (e.g., the use of preventive services such as multiphasic testing [Oakes et al. 1974] and screening [Beaulieu et al. 1996; Edwards and Boules 1997]). Additionally, the suite of relevant confounding factors may differ from outcome to outcome, and for some outcomes there is uncertainty as to the relevant confounding factors. Some of the individual characteristics that affect the decision to start smoking and to continue to smoke also may be determinants of risk for the outcomes considered here.

Figure 6.1 A conceptual model for the relationship between cigarette smoking and diminished health status



Conclusions of Previous Surgeon General's Reports

Extensive research over time has identified cigarette smoking as a cause of specific diseases, and many reports from the Surgeon General have focused on smoking and these diseases. These reports have also addressed more general and nonspecific adverse consequences of smoking, such as increased rates of absenteeism from work or the utilization of medical services among smokers in comparison with nonsmokers. Conclusions from the reports that relate to these outcomes are listed in Table 6.1, including findings on general respiratory morbidity. Reports of increased morbidity from common and frequent viral and bacterial respiratory infections among smokers have been reviewed (U.S. Department of Health and Human Services [USDHHS] 1990) and are among the topics covered in Chapter 4 of this report. However, the overall health status of smokers compared with nonsmokers has not been comprehensively addressed in prior Surgeon General's reports.

Biologic Basis

Cigarette smoke, inhaled through the mouth into the lungs, reaches lung airways and alveoli, where the tobacco smoke components pass into the systemic circulation (Murray 1986). The airways and alveoli themselves are exposed to the gaseous and particulate components of tobacco smoke as many of these components readily pass through the alveolar-capillary membrane into the alveolar capillaries and then circulate throughout the body. Nicotine, for example, which is among these components, reaches the brain within 10 seconds after smoke is inhaled (USDHHS 1988). It is distributed throughout the body and has been found in breast milk (Schwartz-Bickenbach et al. 1987; Schulte-Hobein et al. 1992; Golding 1997) and in cervical mucus (Prokopczyk et al. 1997). Carbon monoxide, a diffusible gas, moves from the alveoli into the capillaries where it binds tightly to the hemoglobin of the red blood cells. Benzo[a]pyrene, a well-characterized carcinogen in tobacco smoke, can be found bound to the blood cells in the epithelial cells of the airways of smokers and in their major organs. The effects of smoking on host defenses and aspects of immune function have been covered in prior reports (USDHHS 1990, 1994) and again in this report. These effects may have the consequence of increasing risks for infections, whether of the respiratory tract or other organs. However, there has been less research to date on infections beyond those of the respiratory tract. This systemic distribution of tobacco smoke components underlies the associations between smoking and disease that are well documented for many organs including cardiovascular disease, stroke,

Table 6.1 Conclusions from previous Surgeon General's reports concerning smoking as a cause of diminished health status and respiratory morbidity

Statement	Surgeon General's report
"...cough, sputum production, or the two combined are consistently more ... among smoking ... non-smokers." (p. 302)	1964
"... cigarette smoking ... [has] ... been shown to increase ... respiratory symptoms ... [and] ... decrease ventilatory function." (p. 33)	1967
"... cigarette smoking ... [has] ... been shown ... that ... smokers ... [have] ... more ... respiratory symptoms ... [and] ... greater ... decrease ... in ventilatory function ... than ... nonsmokers." (p. 4)	1967
"... cigarette smoking ... [has] ... been ... associated with ... respiratory symptoms ... including ... cough, sputum production, and bronchitis ... which ... [are] ... more frequent ... in smokers ..." (pp. 9–10)	1971
"... cigarette smoking ... [has] ... been ... associated with ... respiratory symptoms ... particularly ... chronic bronchitis ... among ... smokers ..." (p. ...)	1971
"... cigarette smoking ... [has] ... been demonstrated ... [to] ... [have] ... substantial ... measures ... [of] ... lung function ... [and] ... [to] ... produce ... more ... [of] ... these ... [in] ... smokers ..." (p. 48)	1972
"... cigarette smoking ... [has] ... been shown to have ... [an] ... effect ... [to] ... impair ... [the] ... ciliary ... [and] ... macrophage ... [activity] ... [which] ... [is] ... [a] ... [defense] ... [against] ... [infection]." (p. 28)	1973
"... cigarette smoking ... [is] ... [a] ... cause of COPD ... cigarette smoking ... [is] ... [a] ... major ... [factor] ... [in] ... [the] ... development ... [of] ... chronic ... [bronchitis] ... [and] ... [in] ... [the] ... development ... [of] ... [emphysema]." (p. 61)	1975
"... [the] ... [risk] ... [of] ... [developing] ... [cancer] ... [of] ... [the] ... [urinary] ... [bladder] ... [is] ... [related] ... [to] ... [cigarette] ... [smoking]." (p. 12)	1979
"... [the] ... [risk] ... [of] ... [developing] ... [cancer] ... [of] ... [the] ... [kidney] ... [is] ... [related] ... [to] ... [cigarette] ... [smoking]." (p. 18)	1979
"... [the] ... [risk] ... [of] ... [developing] ... [cancer] ... [of] ... [the] ... [pancreas] ... [is] ... [related] ... [to] ... [cigarette] ... [smoking]." (p. 19)	1979
"... [the] ... [risk] ... [of] ... [developing] ... [cancer] ... [of] ... [the] ... [esophagus] ... [is] ... [related] ... [to] ... [cigarette] ... [smoking]." (p. 20)	1979

Table 6.1 Continued

Statement	Surgeon General's report
"The relationship between smoking and an increased prevalence of respiratory symptoms in the adult has been well established in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community." (p. 8-20)	1979
"... [in] ... summary, ... [the] ... recent studies ... demonstrate a higher ... [frequency] ... of respiratory symptoms ... [in] ... men ... who ... smoke ... cigarettes ... [than] ... in ... men ... who ... never ... smoked ... [and] ... in ... women ... who ... smoke ... [than] ... in ... women ... who ... never ... smoked ... [and] ... [that] ... these ... relationships ... [are] ... [found] ... [in] ... [both] ... [the] ... [young] ... [adult] ... [and] ... [elderly] ... [age] ... [groups]. ... [The] ... [effect] ... [of] ... [cigarette] ... [smoking] ... [is] ... [one] ... [that] ... [is] ... [related] ... [to] ... [the] ... [number] ... [of] ... [cigarettes] ... [smoked] ... [and] ... [to] ... [the] ... [number] ... [of] ... [years] ... [smoked]." (p. 8-20)	1979
"... [the] ... [relationship] ... [between] ... [smoking] ... [and] ... [cough] ... [or] ... [phlegm] ... [is] ... [one] ... [that] ... [is] ... [well] ... [established]. ... [They] ... [have] ... been ... [a] ... [major] ... [concern] ... [of] ... [epidemiologists] ... [and] ... they ... have ... been ... [the] ... [most] ... [studied] ... [and] ... [are] ... [judged] ... [to] ... [be] ... [causal]." (p. 47)	1984
"... [Overwhelming] ... [evidence] ... [from] ... [population] ... [studies] ... [has] ... [established] ... [that] ... [cigarette] ... [smoking] ... [is] ... [a] ... [cause] ... [of] ... [chronic] ... [bronchitis]."	1984
"... [Smoking] ... [is] ... [associated] ... [with] ... [cough], ... [sputum] ... [production] ... [and] ... [chronic] ... [bronchitis] ... [and] ... [emphysema]."	1984
"... [Current] ... [smokers] ... [have] ... [a] ... [significantly] ... [greater] ... [prevalence] ... [of] ... [chronic] ... [cough] ... [and] ... [phlegm] ... [and] ... [of] ... [chronic] ... [bronchitis] ... [than] ... [do] ... [ex-smokers] ... [or] ... [nonsmokers]. ... [Cigarette] ... [smoking] ... [is] ... [the] ... [most] ... [important] ... [factor] ... [in] ... [the] ... [development] ... [of] ... [chronic] ... [bronchitis] ... [in] ... [the] ... [United] ... [States]."	1989

Source: U.S. Department of Health, Education, and Welfare 1964, 1967, 1971, 1972, 1973; U.S. Department of Health and Human Services 1979, 1984, 1989.

and cancers of the kidney and urinary bladder. The widespread distribution may also lead to more general effects on health.

This same systemic distribution may have nonspecific effects as well, contributing to a reduction in health status. Exposure to tobacco smoke components causes smoke-specific diseases such as bladder cancer (carcinogens in urine come in contact with the bladder) and atherosclerosis, probably reflecting multiple underlying mechanisms with inflammation having a central role (Cross et al. 1999). Underlying mechanisms might include heightened oxidative stress and reduced antioxidant defenses, increased inflammatory activity, reduced host defenses against infection, and lowered reparative capacities of tissues. The evidence on these mechanisms is at varying levels of development. This section focuses on oxidative stress as an example, selected because the available literature is extensive.

Oxidative Stress

Oxidative stress refers to an increased exposure to oxidants and/or a decreased antioxidant capacity, caused by oxygen radicals that mutate DNA, promote atherosclerosis, and lead to chronic lung injury. Oxidative stress is now hypothesized to be a general mechanism underlying aging and many of the chronic diseases associated with aging, contributing to the development of cancer, cardiovascular disease, and COPD (Ames et al. 1993). Mounting evidence points to chronic oxidative stress as one mechanism whereby smoking affects health. Smoking is associated with

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evidence of chronic systemic inflammation, perhaps a consequence of the chronic oxidative stress experienced by the smoker (Cross et al. 1999; Hecht 1999). The oxidant load posed by cigarette smoke is substantial; the tar component is estimated to contain 10^{14} oxygen radicals per gram of tar and the gas component to have as many as 10^{15} other organic radicals per puff (Repine et al. 1997).

A number of comparisons between smokers and nonsmokers have been made with respect to measures of biomolecular oxidative damage, including oxidative injury to DNA, proteins, and lipids. A widely used assay for quantifying oxidative damage to DNA is 8-hydroxydeoxyguanosine (8-OH-dG). The assay measures hydroxyl radical-induced DNA damage at C8 of guanine (Laguzio et al. 1994), which has been linked experimentally to cigarette smoke condensate (Leanderson and Tagesson 1990). Cultured human lung cells exposed to cigarette smoke had 70 percent higher 8-OH-dG levels than unexposed cells (Leanderson and Tagesson 1992). DNA from the lung tissue of smokers had 42 percent higher 8-OH-dG levels than the DNA from nonsmokers, and 8-OH-dG concentrations increased according to the number of cigarettes smoked per day (Asami et al. 1997).

Studies comparing 8-OH-dG levels in DNA from smokers and nonsmokers are summarized in Table 6.2. In general, regardless of the biologic material, smokers tend to have greater damage. A strong dose-response association with the number of cigarettes smoked was observed in one study (Lodovici et al. 2000), but an inverse dose-response trend was observed in another (van Zeeland et al. 1999). When levels of 8-OH-dG in circulating lymphocytes were compared before and after cigarettes were smoked, Kiyosawa and colleagues (1990) observed that 8-OH-dG levels increased 54 percent after smoking. A similar but less frequently used approach to determine biomolecular oxidative damage is to assay 8-hydroxyguanine, which has been found in leukocyte DNA (Asami et al. 1997) and in urine (Suzuki et al. 1885) of smokers at concentrations at least 90 percent higher than in nonsmokers.

Oxidative damage to proteins can occur in both amino acid residues and the peptide backbone in protein, and can be assessed by assaying protein carbonyls (Reznick et al. 1992; Buettner et al. 1995). Studies document that exposing human plasma (Reznick et al. 1992; Buettner et al. 1995; Panda et al. 1999) or saliva (Nagler et al. 2000) to cigarette smoke increased protein carbonyl concentrations by more than 300 percent. Compared with unexposed guinea pigs, guinea pigs exposed to cigarette smoke had plasma protein carbonyl concentrations more than 30 times greater (Panda et al. 2000). In humans, protein carbonyl concentrations in 15 smokers were 61 percent higher than in 5 comparison nonsmokers (Lee et al. 1998).

Isoprostanes constitute a specific measure of lipid peroxidation and serve as good general markers of oxidative injury (Morrow and Roberts 1996). Free radicals catalyze the peroxidation of arachidonic acid to F2-isoprostanes (Morrow and Roberts 1998). Circulating (Morrow et al. 1995) and urinary (Morrow et al. 1995; Reilly et al. 1996) isoprostane levels have been shown to be markedly higher in smokers than in nonsmokers (Table 6.2). Circulating (Morrow et al. 1995; Pilz et al. 2000) and urinary (Reilly et al. 1996; Pilz et al. 2000) isoprostane concentrations decreased at least 20 percent within two weeks of smoking cessation. Babies of smoking mothers had concentrations of isoprostane levels in their umbilical arteries and veins more than 110 percent higher than babies of nonsmoking mothers (Obwegeser et al. 1999).

Another widely used measure of free radical catalyzed lipid peroxidation is thiobarbituric acid reactive substances (TBARS) (Bonithon-Kopp et al. 1997). Comparisons of TBARS between smokers and nonsmokers have shown that (1) current smokers have higher TBARS levels—sometimes strikingly higher, (2) levels of TBARS rise after smoking, and (3) the influence of smoking on increased lipid peroxidation can be offset somewhat by administering the antioxidant micronutrients vitamins C and E (Table 6.2).

Antioxidant Depletion

Even as smokers are exposed to the oxidative stress of regularly inhaling cigarette smoke, substantial evidence shows that blood levels of individual antioxidant micronutrients are lower in current smokers than in nonsmokers. This association has been clearly demonstrated for vitamin C (McClean et al. 1978; Bolton-Smith et al. 1992; Rexa et al. 1995; Lykkesfeldt et al. 1997) and for total and selected carotenoids including α-carotene, β-carotene, and cryptoxanthin (Aoki et al. 1987; Snyder et al. 1988; Bolton-Smith et al. 1991; Pamuk et al. 1994; Ross et al. 1995; Brady et al. 1996; Alberg et al. 2000). For vitamin C (Brook and Grimshaw 1968; Buiatti et al. 1996; Marangon et al. 1998) and several of the specific carotenoids (Comstock et al. 1988; Nierenberg et al. 1989; Buiatti et al. 1996; Marangon et al. 1998), circulating concentrations tend to decline with increasing number of cigarettes smoked.

Table 6.2 Studies on the association between smoking and oxidative injury

Study	Population	Group
8-OH-dG[a] in DNA from peripheral leukocytes		
Kiyosawa et al. 1990	10 healthy male volunteers, aged 20–22 years, blood drawn before and 10 minutes after smoking 2 cigarettes *in 10 minutes*	Total
[illegible] et al. 1994	20 healthy male factory workers, aged 25–58 years	Current and never Former and never
Degan [illegible] 1996	187 smokers and nonsmokers	Total
[illegible] et al. 1998	20 healthy volunteers, 10 smokers, aged 19–23 years	Total
van Zeeland [illegible] 1999	102 healthy individuals aged 20–45 years	Current and never Former and never
[illegible] et al. 2001	56 healthy nonsmoker volunteers, aged 18–63 years	Current and never Former and never
8-OH-dG in DNA from urine		
Loft [illegible] 1992	83 male and female subjects, aged 40–64 years	Total
Tuppurainen et al. 1993	227 persons (32 dissection employees, 75 timber workers, 70 controls, 50 dairy workers, 40 controls)	Total Controls Asbestos-exposed workers Smokers
Lagunio et al. 1994	5 smokers (1 sample/1 day) and 5 nonsmokers (2 samples/2 days)	Current and never Former and never
Tuppurainen et al. 1998	342 workers from the Swedish agriculture industry	Total Men Women
Protein carbonyls in plasma		
Lee et al. 1998	20 healthy volunteers, 15 smokers, aged 19–58 years	Total

[a]8-OH-dG = 8-hydroxydeoxyguanosine.

Results			
Precessation	Postcessation	Percentage difference	Comments
3.3 (before smoking)	5.1 (after smoking)	[illegible]	8-OH-dG/10^6 dG
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
2.13	3.20	50.2	8-OH-dG pmol/24 hours
[illegible]	[illegible]	[illegible]	Weighted average, 8-OH-dG pmol/μmol creatinine
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
1.59	2.56	61.0	Protein carbonyl/nmol/mg of protein

Table 6.2 Continued

Study	Population	Group
Isoprostanes in plasma		
Morrow et al. 1995	Pilot: 16 smokers, 8 nonsmokers Main study: [illegible] 10 age- and gender-m[illegible] d[illegible] smokers	Pilot: free Pilot: esterified Main: free Main: esterified Main: correlation, free Main: correlation, esterified
[illegible] et al. 2000	4[illegible] smokers	Total: [illegible] pg/mL
Isoprostanes in urine		
Morrow et al. 1995	20 smokers (1 age- and gender-matched nonsmoker)	Total
[illegible] et al. 1996	24 female smokers (24 age- and [illegible] nonsmoker controls), aged 23–47 years	Total Mid-luteal Luteal Nonsmoker
[illegible] et al. 1998	6 smokers (cessation [illegible] years), aged 41–44 years	Total [illegible] pg/mL creatinine Total 8-iso-PGF[illegible] pg/mL creatinine
Pilz et al. 2000	47 smokers (continuing smoking and [illegible] cessation), aged 20–60 years	Total [illegible]
Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)		
Harats et al. 1989	16 smokers, 12 age-matched nonsmokers, aged 23–56 years	Total (stored) Total (fresh)

[a]LDL = Low-density lipoprotein.

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Results			
Precessation	Postcessation	Percentage difference	Comments
90	166	84.4	
290	496	71.0	
103	242	135.0	
345	574	66.4	
250	156	60.3	2 weeks after cessation
624	469	33.0	
150	90	60.0	nmol/L [term illegible] 4 weeks after cessation
410	870	112.0	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
0.287	0.198	44.8	Smokers had not smoked for 24–48 hours
0.180	0.154	16.9	Plasma: nmol/mL LDL: nmol/mg protein

Table 6.2 Continued

Study	Population	Group
Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)		
Harats et al. 1990	17 smokers before and 2 weeks after vitamin C supplementation; 10 smokers before and 90 minutes after smoking	Study I No treatment Vitamin C treatment Study II: TBARS in LDL No treatment Vitamin C treatment Vitamin E treatment Study II: Plasma TBARS No treatment Vitamin C treatment Vitamin E treatment
Scheffler et al. 1994	17 male smokers, 21 male nonsmokers, [illegible]	[illegible] [illegible] 0 hours 1 hour 2 hours 3 hours 4 hours 5 hours 6 hours
Schettler et al. 1992	17 smokers, 21 nonsmokers	[illegible] [illegible]
Dhalla et al. 1993	242 adults, aged 45–69 years	Total
Miller et al. 1997	167 nonsmokers, 14 smokers, [illegible]	Total
Moore et al. 1997	[illegible] aged 35–60 years	Total [illegible]
Moore et al. 1997	47 healthy male nonsmokers, 20 [illegible] aged 21–25 years	Total Smokers pre-[illegible] smoking
Pryor 1998	74 men and 74 women, [illegible]	Men Women
Dhalla et al. 1993	91 adults, aged 25–81 years	Total

Results			
Precessation	Postcessation	Percentage difference	Comments
Before smoking	After smoking		Plasma: nmol/mL
0.108	0.187	76.4	LDL: nmol/mg protein
0.138	0.145	5.1	
0.584	1.275	118.3	
0.883	1.333	95.2	
[illegible]	[illegible]	5.7	
[illegible]	0.197	85.4	
[illegible]	0.118	10.3	
[illegible]	[illegible]	3.4	
[illegible]	[illegible]	[illegible]	[illegible] nmol/mL
1	1	0	
1	2	1	
3	4	125	
[illegible]	[illegible]	100	
[illegible]	[illegible]	100	
[illegible]	[illegible]	100	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	170	[illegible]	nmol/mL
64	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	LDL: [illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
0.55	0.31	77.4	mmol/L [illegible]

Whether the differences in antioxidant levels across smoking categories reflect direct depletion or differing dietary intake has been controversial. If smoking directly depletes antioxidant micronutrients, the effect would presumably be acute. In fact, levels of vitamin C and selected carotenoids increased when measured in persons after 84 hours without smoking a cigarette (Brown 1998), and an experimental exposure of plasma equivalent to six puffs of cigarette smoke completely depleted the ascorbic acid present in the serum (Handelman et al. 1991; Biserich et al. 1995). When measurements were taken at baseline and 20 minutes after smoking a cigarette, decreases in circulating micronutrient concentrations were observed (Yeung 1976).

Smoking and the Leukocyte Count

Studies show that smokers when compared with nonsmokers have generally heightened inflammation, increased white blood cell counts that remain elevated after cessation, and increased levels of other markers of inflammation such as C-reactive protein (Allen et al. 1985; Das 1985; de Maat et al. 1996; Tracy et al. 1997; Danesh et al. 1999).

The association between smoking and the leukocyte count has been extensively investigated, with numerous studies showing that current smokers have higher leukocyte counts than nonsmokers (Table 6.3). In most studies, the increase was 20 percent or more in smokers compared with nonsmokers and was present across strata of age, gender, and race. The leukocyte count increases with the number of cigarettes smoked per day and with the depth of inhalation. Similar dose-response trends were evident in other studies that did not lend themselves to inclusion in the summary tables (Petitti and Kipp 1986; Schwartz and Weiss 1991). Dose-response trends tend to be weaker when examined in relation to either pack-years[1] or duration of smoking, suggesting that smoking has an immediate effect on the leukocyte count.

The findings from former smokers are consistent with both an immediate and a persistent effect of smoking. In comparisons with lifetime nonsmokers (Table 6.4), former smokers consistently have higher white blood cell counts, but the difference is smaller than that between current smokers and lifetime nonsmokers. In most of the studies, the leukocyte counts for former smokers were only about 5 percent greater than those for lifetime nonsmokers. The excess is persistent (Petitti and Kipp 1986; Schwartz and Weiss 1991; Sunyer et al. 1996), although it decreases with increasing duration of cessation, becoming closer to the average counts found in lifetime nonsmokers (Yarnell et al. 1987; Hansen et al. 1990b). A short-term (overnight) abstention from cigarettes did not strongly influence the counts (Noble and Penny 1975).

Prospective cohort studies have tracked changes in leukocyte counts in relation to changes in smoking. In a study of Kaiser Permanente enrollees in the San Francisco Bay area, the leukocyte counts increased 12 percent among those who started smoking during the follow-up, but it decreased 7 percent among smokers who had quit during the follow-up (Friedman et al. 1973). In a subsequent study that compared leukocyte counts of 9,392 persistent smokers with those of 3,825 smokers who had quit, the quitters experienced significantly higher declines (Friedman and Siegelaub 1980). In a cohort of homosexual men seronegative for human immunodeficiency virus (HIV), Sunyer and colleagues (1996) observed that decreases in smoking were followed by decreased white blood cell counts, and increases in smoking were followed by increased white blood cell counts. Furthermore, changes in white blood cell counts were proportional to changes in smoking patterns (Table 6.5).

These observations of inflammatory markers, particularly the leukocyte counts, are consistent with the induction of systemic chronic inflammation in smokers, perhaps reflecting the substantial oxidant load from habitual cigarette smoking. Studies of former smokers suggest that this state of inflammation does not simply reflect an acute effect. These observations support one of the mechanisms, oxidative stress, proposed as contributing to the general effects of smoking on health.

Epidemiologic Evidence

Absenteeism

Absenteeism from work is frequent and costly (Steers and Rhodes 1978); its multiple causes include individual and organizational factors (Steers and Rhodes 1978). Researchers investigating the effect of smoking on absenteeism face the challenges of controlling for potential confounding by individual-level factors such as alcoholism, and specifying how smoking could act in combination with other factors at both

[1] Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

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individual and group levels. While the literature is extensive (Table 6.6), the studies vary in the success with which these challenges have been met, partially reflecting the extent and quality of available data.

Current Smokers

In studies with varying designs conducted in diverse locations, cigarette smokers consistently have had higher rates of absenteeism than nonsmokers (*Table 6.6*). *The evidence also indicates that the duration* of sickness absences tends to be longer for smokers and smokers miss more cumulative worktime than nonsmokers. The association between smoking and absenteeism has been observed in both men and women of all ages. Sickness absences have been measured in a variety of ways, including lost worktime per unit of time (e.g., "absence rate") and the duration of absences. The finding that smoking is associated with absenteeism regardless of the index used, documents the consistency of the observed association. Although most studies were cross-sectional or retrospective in design, two were prospective cohort studies (North et al. 1993; Niedhammer et al. 1998) and another studied smoking histories in relation to workplace attendance records during the preceding nine years (Holcomb and Meigs 1972). *The findings of these* prospective studies confirm that smoking preceded the absenteeism. In a few studies, the association with smoking was observed primarily in men but not in women (Green et al. 1992; North et al. 1993), but in general the findings have been consistent across all of the subgroups studied. Of the 30 studies that were the sources for the data abstracted into Table 6.6, 17 studies found that absenteeism among smokers was at least 20 percent greater than among nonsmokers in all subgroups.

Two additional reports not included in the table also provide evidence of an association between smoking and absence frequency (Ferguson 1973; Donaldson et al. 1999). In a study of 516 men employed in four occupational groups in Australia, Ferguson noted that "... the employee with repeated absence also tended ($p < 0.10$) more often than the resister" (employee without repeated absences) "... to smoke more than 15 cigarettes daily" (Ferguson 1973, p. 336). In a study of 146 lumber company employees, a tobacco use scale was not correlated ($r = 0.01$) with absenteeism (Donaldson et al. 1999).

In several studies summarized in Table 6.6 that assessed the relationship between current smoking and absenteeism (Athanasou 1979; Andersson and Malmgren 1986; Hawker and Hultby 1988; Bertern 1991), current smokers were compared with all *nonsmokers, including former smokers. As discussed* in the following section, absenteeism rates among former smokers are persistently elevated compared with those of lifetime nonsmokers. Thus, using an "unexposed" comparison category that includes former smokers along with lifetime nonsmokers will dilute associations that would be estimated when using a *"pure" unexposed category consisting solely of per*sons who have never smoked.

In the two studies that assessed the dose-response relationship with the number of cigarettes smoked, the likelihood of being absent increased strongly with the number of cigarettes smoked per day (Lowe 1960; Holcomb and Meigs 1972). In a retrospective cohort *study of 226 male factory employees in Connecticut* that included eight years of follow-up, the rate of long-term absences increased 43 percent, 57 percent, and 100 percent compared with nonsmokers for those who smoked less than one pack, one pack, and more than one pack of cigarettes per day, respectively (Holcomb and Meigs 1972). In a study of more than 3,300 male General Electric employees in England, the number of days absent for medical reasons increased 11 percent, 13 percent, 26 percent, and 57 percent compared with nonsmokers for those who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes per day, respectively (Lowe 1960).

This body of evidence shows increased absenteeism among smokers, *while providing only limited* information on the reasons for the absences. A significant proportion of sickness absences in smokers would be expected to be due to smoking-associated illnesses. Athanasou and colleagues (1981) hypothesized that smoking acts as a susceptibility factor, increasing the risks for other harmful occupational exposures. In one *study, smoking was associated with a significantly in*creased likelihood of absences resulting from problems as diverse as back symptoms, digestive tract symptoms, and neck and upper limb symptoms (Dimberg et al. 1999). A recent review summarizing 28 studies showed an increased risk for back pain in smokers compared with nonsmokers in the majority of studies (Goldberg *et al. 2000). In another study,* absences were elevated not only for "medical reasons" but also for "other" reasons (Lowe 1960). Substantial evidence also documents that smokers are more likely than nonsmokers to have on-the-job injuries (Lowe 1960; Naus et al. 1966; Reynolds et al. 1994; Forrester et al. 1996). Because smoking increases absences for a broad set *of health problems, and not just specific* smoking-associated illnesses, the underlying causal pathways are likely to be multiple and general, reflecting the systemic nature of the effects of smoking.

Table 6.3 *Studies on the association between current smoking and white blood cell counts*

Study	Population	Group
Howell 1970	2,483 men, aged 40–64 years	Total
[illegible] et al. 1971	4,284 men, aged 46–52 years	Total
Fried[illegible] et al. 1979	88,488 Kaiser Permanente members	Men Women
Oliveri[illegible] 1979	185 factory workers, age 20–56 years	Total
Farukhi et al. 1981	120 Indian men, aged 18–64 years	Total
Bridgeman et al. 1985	121 university students	Men Women
Friedman and Rosenman 1985	3,401 executives, aged 39–59 years	Total
Niedhammer, Kostenzer, et al. 1998	868 healthy patients, aged 20–65 years	Men Women
Smith and Peters 1985	43 police officers, [illegible] years	Total
Parekh et al. 1985	535 Indian men, age 20–49 years	Total
Nilsson et al. 1985	263 [illegible] Sea, 221 [illegible] years	Total
Dickinson et al. 1986	1,462 Scottish men, aged 58–68 years	Total
Dodswo[illegible] et al. 1987	931 [illegible] men, aged 18–[illegible] years	Men Women
Zeldin et al. 1988	9,205 men, aged 45–[illegible] years, Finland	Total
Hjelmgren et al. 1988	90 male students	Total
Mc[illegible]son et al. 1988	449 men, age 70 years, Göteborg, Sweden	Total
Naus et al. 1989	100 male smokers, 78 ex-smokers, 100 nonsmokers	Total
Chan-Yeung et al. 1994	2 cohorts of [illegible] aluminum smelter workers 442 office workers, Edmonton, Canada	Plant [illegible] Total
Sparrow et al. 1994	1,510 men, aged 21–[illegible] years	Total

Results (white blood cell counts)			
Smokers	Nonsmokers	Percentage difference	Comments
7,257	5,819	24.7	Per mm³ of blood
6,549	5,705	14.8	Per mm³ of blood
8.2	7.1	[illegible]	[illegible] per cubic millimeter
8.3	7.3	13.7	[illegible] per cubic millimeter
6,738	5,440	23.9	Per mm³ of blood weighted average for smokers
6,868	[illegible]	[illegible]	Per mm³ of blood
6.0	[illegible]	15.3	[illegible] per mm³ of blood
7.0	5.8	20.7	[illegible] per mm³ of blood
7.59	6.26	[illegible]	[illegible] per mm³ of blood weighted average
7.7	7.1	8.4	[illegible] per mm³ of blood
6.5	5.1	27.4	[illegible] per mm³ of blood weighted average
[illegible]	[illegible]	24.2	Per mm³ of blood
[illegible]	[illegible]	24.7	Per mm³ of blood
[illegible]	[illegible]	[illegible]	Per mm³ of blood
6.1	4.9	24.5	[illegible] per mm³ of blood weighted average for smokers
7.2	6.1	[illegible]	[illegible] per mm³ of blood
7.2	6.1	18.0	[illegible] per mm³ of blood
5,740	7,284	21.2	[illegible] per mm³ of blood
[illegible]	[illegible]	12.1	[illegible] per mm³ of blood
[illegible]	[illegible]	18.1	[illegible] per mm³ of blood
9.1	[illegible]	25.5	Per mm³ of blood
8.4	[illegible]	25.4	[illegible] per mm³ of blood
7.6	[illegible]	26.0	[illegible] per mm³ of blood weighted average
8,400	6,836	23.0	Per mm³ of blood: weighted average for smokers

Table 6.3 Continued

Study	Population	Group
Vanuxe[illegible] et al. 1984	4[illegible] France	Total
Cu[illegible]ano 1985	35,000 [illegible], aged 20–60 years	Men Women
Ne[illegible]son 1985	82 [illegible] students, aged 18–24 years	Total
Hong Kong Population 1987	9[illegible] men, mean age 58 years	Total
Yarn[illegible] et al. 1988	1,[illegible] men, aged 18–[illegible] years, from a [illegible] in the United Kingdom	[illegible] [illegible]
Chan-Yeung et al. 1988	700 male aluminum smelter workers	Total
Hanss[illegible] et al. 1989	2,668 men, aged 51–[illegible] years	Total
Olsen et al. 1991	1,900 Body Mechanics Study participants	Men Women
[illegible]ovanovic et al. 1992	102 military academy cadets, mean age [illegible]	Total
Muhlbaier et al. 1993	248 soldiers, [illegible]	Men Women
Mercuria-Rodriguez et al. 1994	71[illegible] pregnant women	Total
Hockey et al. 1996	6,837 clerical workers, mean age 58 years	Men Women
Bovill et al. 1996	9,[illegible] persons, ages 45–64 years	Men Women
Chiesi et al. 1998	2[illegible] teenagers, new to participants[illegible] for smoking	Total
Jensen et al. 1998	484 persons	Total

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Results (white blood cell counts)			
Smokers	Nonsmokers	Percentage difference	Comments
[illegible]	5.8	37.9	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	4	5	6	Comments
0	22.0	30.1	NR*	NR	NR	NR	None
0	6.2	33.5	NR	NR	NR	NR	None
0	7	7.4	2.5	10.0	NR	NR	
0	20.8	23.5	27.7	29.7	NR	NR	
0	18.0	32.5	NR	NR	NR	NR	
0	19.5	28.1	NR	NR	NR	NR	Weighted average
0	7.1	10.8	NR	NR	NR	NR	None
0	3.7	14.0	16.5	16.3	NR	NR	
0	29.1	28.7	40.1	29.9	NR	NR	
0	6.6	12.0	15.0	14.2	21.2	27.2	None
0	7.6	21.0	25.0	34.1	NR	NR	None
0	7.0	6.5	12.7	14.7	21.3	NR	None
0	8.9	13.3	19.1	20.4	31.1	NR	
0	5.1	20.6	19.0	24.5	25.5	NR	None
NF	12.0	24.6	25.3	33.5	NR	NR	
0	9.3	26.4	26.8	NR	NR	NR	None
0	5.8	11.5	NR	NR	NR	NR	None
0	5.4	16.3	19.9	NR	29.8	NR	
0	20.3	17.9	25.4	23.6	31.3	NR	None
0	6.5	9.0	21.1	22.0	17.7	NR	
0	19.0	33.3	21.2	14.3	23.3	NR	
0	4.1	10.4	13.4	20.1	17.4	NR	
0	4.0	20.8	NR	NR	NR	NR	None
0	21.9	20.8	43.6	49.0	54.4	NR	None

Table 6.5 Continued

Study	Population	Measure of dose	Group
Yarnell et al. 1987	4,445 men, aged 45–59 years, in 2 communities	Number of cigarettes/day	Caerphilly Speedwell
Chang-Yeung et al. 1984	750 male & alu aloom & rubber workers	Number of cigarettes/day	Total
Hilgard et al. 1986	2,340 men aged 15–64 years	Number of cigarettes/day Inhalation*	Total Total
Olsen et al. 1981	3,805 Danes (response 0.85–0.89) 45,650 twins	Number of cigarettes/day Pack-years†	Men Women Men Women
Surgeon et al. 1986	2,446 patients aged 25–55 years	Number of cigarettes/day	Total
Jarvis et al. 1988‡	4,114 (84) smokers, 156 ex-smokers	Number of cigarettes/day	Total

*Inhalation = inhaling cigarette smoke.
†Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Former Smokers

The evidence is consistent that former smokers are less likely to be absent from work compared with persistent smokers. Former smokers tend to have somewhat higher absenteeism rates than persons who have never smoked (Table 6.7), but the increases are much smaller than those for current smokers. The analyses performed by Wooden and Bush (1995) with former smokers (n = 4,812) in the 1989–1990 Australian National Health Survey illustrate the seemingly *paradoxic relationship between quitting smoking and absenteeism.* In a multiple regression model that included both the duration of active smoking and time since quitting, the number of years that a former smoker had smoked remained a strong predictor of absenteeism, and the likelihood of absences declined gradually over time since cessation (Wooden and Bush 1995). Similarly, Manning and colleagues (1989) found differences between recent and sustained quitters, and observed considerably higher absenteeism rates for recent quitters compared with long-term quitters. These results indicate that both prior smoking history and time since quitting are factors strongly associated with absenteeism, but in opposite directions. This pattern may arise because some smokers may quit when diagnosed with an illness caused by smoking, and the recent quitters may thus already have a smoking-induced illness that predisposes them to lost worktime.

In interpreting evidence linking smoking to a diminished health status, including absenteeism, untangling the direct effects of smoking from the indirect effects is challenging, as smokers and nonsmokers may differ in potential confounding factors. Nonetheless, given the scope of the evidence available and the diversity of the populations studied, the literature does provide insights into the role of smoking as a cause of absenteeism.

With regard to confounding, alcohol use is a major factor of concern. Alcohol use has been linked to absenteeism in some studies, and smokers drink more than nonsmokers (Smith 1970; Turner 1988; Ault

Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	4	5	6	Comments
0	30.4	37.2	40.1	NR	NR	NR	None
0	39.4	38.4	41.8	NR	NR	NR	
0	27.0	24.2	28.0	NR	NR	NR	None
0	21.5	22.1	25.5	25.2	36.7	NR	None
0	12.9	15.6	19.7	25.3	27.0	NR	
0	21.8	12.0	45.6	NR	NR	NR	None
0	22.2	21.9	31.1	NR	NR	NR	
0	31.3	26.3	32.5	42.4	NR	NR	
0	8.7	29.4	24.1	34.5	NR	NR	
0	7.1	13.7	25.0	31.1	NR	NR	None
0	31.0	40.6	NR	NR	NR	NR	None

et al. 1993; Marmot et al. 1995; Vasse et al. 1998). Smokers are also more likely to be heavy alcohol drinkers and to use illicit substances (Merrill et al. 1999; Best et al. 2000; Brain et al. 2000; Dawson 2000), and heavy alcohol and illicit substance use, rather than cigarette smoking, could increase the likelihood of workplace absences. *Studies that adjusted for alcohol consumption* have generally (Hendrix and Taylor 1987; Bush and Wooden 1995; Wooden and Bush 1995), but not *universally (Ault et al. 1991),* found smoking to be associated with frequent absences, implying that the association of smoking with alcoholism is not due to confounding. *Studies were not found* that accounted for illicit substance use in assessing the association between smoking and workplace absences. Less likely *is the possibility that* the association between smoking and absences reflects confounding by characteristics that are linked both to smoking (see the section on "Health Status" later in this section) and to an increased risk for frequent absences. For example, women are consistently absent from work more often *than men (Leigh 1983; Pines et al. 1985; Steinhardt et* al. 1991). But women assume a disproportionate share of family responsibilities such as staying home with *sick children,* and the relative importance of smoking may therefore be less. Observations of persons with "psychosocial problems" (Leigon and Mikaelsson 1984) and anxiety/neuroses (Taylor 1968; Ferguson 1973) document increased risks for absenteeism, and if such persons are more likely to smoke, confounding is possible. Given the range of populations studied, confounding by psychosocial factors seems unlikely.

Of the relevant pathway factors leading to health-related absences, age is the primary demographic characteristic that is a potential modifying or confounding factor. Socioeconomic status, another potential confounding or modifying factor, is inherently restricted in studies within occupational groups. Age is associated with both absenteeism (Pines et al. 1985) and health status. The association between smoking and absenteeism has been observed consistently across a broad spectrum of age strata in the summarized

Table 6.6 Studies on the association between current smoking and absenteeism

Study	Population	Group
Lowe 1960	3,341 male General Electric Company employees, England	Total Medical reasons Other reasons
Hedges and Mergo 1972	225 male factory employees	Total
Wilson 1973	1970 National Health Interview Survey persons aged ≥17 years	Total Men Women 17–44 years 45–64 years ≥65 years
Arthur et al. 1978	474 persons aged [illegible] years	Men Women
U.S. Department of Health and Human Services 1980	Employment sample of U.S. population, aged ≥17 years	1965 Men Women 1977 Men Women
Jamison et al. 1981	1,077 Swedish men aged 47–49 years	Total
Smith et al. 1981	926 staff members from 12 Australian organizations	Men Women

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
Number of days absent during the year			None
11.19	9.81	4.1	
6.59	5.49	[illegible]	
4.61	4.32	[illegible]	
Total days lost per person-year			Short-term: ≥7 days reported for medical assistance
8.02	4.62	[illegible]	Long-term: 210 days or more lost in total combined during 1963–1965
Mean time lost: short-term			
0.58	0.38	[illegible]	
Days lost: short-term			
[illegible]	0.3	46.9	
Mean time lost: long-term			
[illegible]	[illegible]	42.0	
Days lost: long-term			
5.46	3.97	[illegible]	
Mean workdays lost			None
6.3	5.1	[illegible]	
5.8	5.2	[illegible]	
7.4	5.1	[illegible]	
5.8	5.4	[illegible]	
7.5	5.2	[illegible]	
7.7	5.1	[illegible]	
Participating in leisure-time physical activity			Nonsmokers include former smokers plus current smokers
1.12	[illegible]	50.7	
1.00	0.81	[illegible]	
Work-loss days per person due to illness and injury per currently employed persons			None
5.9	4.6	28.3	
6.6	4.8	37.5	
4.9	4.2	40.5	
6.6	5.7	15.8	
Current workers who used sick leave (5 days or more during the year)			Women
1.1	1	[illegible]	
Mean number of days of work			Relative days of work for smokers compared with nonsmokers
1.10	1.0	50.0	
1.36	1.0	36.0	

Table 6.6 Continued

Study	Population	Group
Leigh 1983	1,200 participants in the 1973 Quality of Employment survey, based on a nationwide probability sample	Men White collar Blue collar *Women* White collar Blue collar
Pedersen 1983	221 working women (ages 28–55 years)	Total
Aronson and Aman Malmgren 1980	1,[illegible] Swedish women (ages 20–64 years)	Working women Students
Vitti Tolassi and Lauri 1986	400 Montreal Department of Health employees	Total Men Women
Hendrick and Tasker 1987	462 U.S. airport police officers	Total
Dirkx et al. 1983	1,224 army recruits in basic training	Total
Hawker 1988	[illegible] female nurses	Total
Duijkers et al. 1983	2,8[illegible] Volvo employees, [illegible]	Total
Gentile 1984	Delivery and power industrial employees, [illegible]	Sick leave records Time lost Days lost records
Manning et al. 1989	574 employees of 2 companies, ages 20–75 years	Total sick leave Short-term Long-term

[illegible] data

Results			
Smokers	Nonsmokers	Percentage difference	Comments
Mean number of absences during the past 2 weeks			OR*
1.07	1.0	7.0	
0.72	1.0	-28.0	
1.50	1.0	50.0	
1.99	1.0	99.0	
1.23	1.0	[illegible]	
2.[illegible]	[illegible]	[illegible]	
Mean number of days missed during 6 months			None
3.46	[illegible]	[illegible]	
Mean number of absences			Smokers include former smokers plus current smokers
26	24	[illegible]	
20	[illegible]	[illegible]	
Mean number of sick days per worker			None
[illegible]	3.1	[illegible]	
4.5	4.7	[illegible]	
5.4	4.2	[illegible]	
Average number of work days lost due to illness			None
3.7	2.5	[illegible]	
Missing work with the flu or illness related to upper respiratory infections (flu/sinus disease)			Short-term: person-days of military smokers controlled for exposure
[illegible]	[illegible]	26.9	
Percentage of days missed			Some smokers include former smokers plus current smokers
37.5	[illegible]	[illegible]	
Average days absent in 1 year			Value
21	14	[illegible]	
Missed work, days in last year			Lost all or part of work [illegible] to study-related problems
5.1	4.1	[illegible]	
[illegible]	[illegible]	[illegible]	
Mean hours absent per month			Short-term: ≤2 days
2.13	1.65	[illegible]	Long-term: >2 days
7.44	6.76	[illegible]	
[illegible]	[illegible]	[illegible]	
1.9[illegible]	1.[illegible]	[illegible]	

Table 6.6 Continued

Study	Population	Group
Batenburg and Reinken 1990	907 employees from 4 worksites, employed at least 12 months	Men by age Total <20 years 20–29 years 30–39 years 40–49 years ≥50 years Women by age *Total* <30 years 30–39 years ≥40 years
Jones et al. 1991	1,893 Johnson & Johnson Company employees, aged 21–[illegible] years	1972 1[illegible] 1981
Aultman 1991	2,300 [illegible] 500 [illegible] [illegible] 11% [illegible] [illegible] [illegible]	Total
Bartlett 1991	45,396 Exxon employees	Total Total
Low and Mitchell 1991	30 steel foundry workers, mean age 33.[illegible] years	*Total* *Total* *Total*
Greenberg et al. 1992	8,[illegible] [illegible] of 21 Israeli localities, aged 20–64 years	Men 20–34 years 45–64 years Women 20–44 years 45–64 years Men 20–44 years 45–64 years Women 20–44 years 45–64 years

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
Sickness absence hours			Authors noted that male nonsmokers aged ≥50 years had medical conditions predisposing them to absenteeism
3.9	3.5	11.4	
3.7	3.4	8.8	
4.0	3.6	11.1	
4.0	3.3	21.2	
3.8	2.9	24.1	
3.8	4.5	-13.3	
3.6	3.1	16.1	
3.0	2.1	42.9	
3.8	2.7	40.7	
4.1	3.9	12.9	
Mean sick leave per year			None
4[illegible]	2[illegible]	[illegible]	
[illegible]	[illegible]	40.1	
3[illegible]	[illegible]	20.6	
Days absent from work			The authors noted that the effects of other factors besides smoking were properly assessed
9.7	6.9	2.0	
Mean annual illness days			Nonsmokers include former smokers plus current smokers
2.0	1.2	5.3	
Mean and [illegible] days			
33.67–37	31.00–33	31.0	
Mean number of sick episodes per employee per year			Differences between the total per-smoker difference and the sum of the results for the number and duration of absence episodes
0.9	0.8	20.0	
Mean number of episodes per year			
2.4	1.3	1.0	
Total days absent during the year			
6.0	4.1	31.1	
Mean days absent (2 years)			Three percentages derived in studies were adjusted for age and/or education and other presumed causes of illness
9.09	7.53	20.7	
8.27	6.64	24.5	
14.45	11.17	29.4	
14.79	16.28	-9.5	
13.01	13.04	-0.1	
17.49	13.97	25.2	
Mean days per absence episode			
5.17	4.65	11.2	
10.05	7.41	35.6	
3.66	3.04	4.7	
7.00	7.00	0.0	

Table 6.6 Continued

Study	Population	Group
Ryan et al. 1992, 1996	2,537 U.S. Postal Service employees	Total 1-year follow-up 2-year follow-up
Nerhot et al. 1992	10,314 Gaullaire civil servants, ages 35–59 years, participating in [illegible]	Men Women Men Women
Hagburg and Warner 1994	[illegible] Society of Health Insurance Workers who enrolled in [illegible]	Total
Dalton et al. 1994	405 workers aged 40–65 years and 1,142 managers ages 35–65 years, identified in [illegible] Educational Assurances	Clerks Managers
Ensel and Woodson 1995	1989 National Survey of Health Interview (n = 23,935 employed persons from [illegible] clinics selected household)	Men Women
Tsai et al. 1995	2,287 [illegible] Company employees, mean age 36 years	Men Women Men Women
Niedhammer et al. 1998	12,185 men aged 40–50 years and women (age 40–50 years), prospective cohort	Men Women Men Women

Results			
Smokers	Nonsmokers	Percentage difference	Comments
Mean absence rate			None
5.4	4.1	31.7	
7.9	5.8	36.2	
Periods of absence (short)			Authors noted that the [illegible] effect [illegible] absences, long-term serious illness [illegible] absences
1.40	1.0	40.0	
1.09	1.0	9.0	
Periods of absence (long)			
1.87	1.0	87.0	
1.37	1.0	37.0	
Work loss days per 2 weeks			
1.49	1.0	49.0	1.46
Limitation of [illegible] work			
1.27	1.0	27.1	1.59
Absence prevalence rate			
0.39	1.0	-121.0	1.91
0.61	1.0	-64.0	1.62
Annual number of [illegible]			Adjusted for [illegible] and health status and [illegible]
1.43	1.0	43.0	
1.42	1.0	42.0	
Average duration of absence (days)			None
7.1	4.1	73.2	
5.8	3.8	52.6	
Mortality [illegible] rate			
2.35	1.0	134.6	
2.74	1.0	174.0	
Periods of absence			Adjusted rate ratios
1.24	1.0	24.0	
1.26	1.0	26.0	
Absence days			
1.45	1.0	45.0	
1.26	1.0	26.0	

results, implying that the association does not reflect confounding by age.

Only a few studies provide prospective data concerning absenteeism following smoking cessation; the findings suggest that smoking cessation is associated with better attendance at work. A particularly informative study conducted with employees of a North Carolina pharmaceutical company compared the attendance patterns of former smokers before and after quitting with attendance patterns of a matched group of persistent smokers (Jackson et al. 1989). In the time preceding smoking cessation by the cessation group, the persistent smokers tended to have fewer absences than the smokers who went on to stop smoking. However, during the three years following cessation, the mean number of annual sick days declined among those who quit. Absences continued to increase for persistent smokers, leading to a widening gap in absences between the two groups. The study was small, with only 70 persons participating. In a randomized trial of nine worksite smoking cessation programs, employees who were smokers at baseline had a significant reduction ($p = 0.002$) in self-reported sick days after stopping smoking (Jeffrey et al. 1993). In another study evaluating a workplace health promotion program that reduced smoking prevalence, the authors reported significant reductions in absenteeism for program participants but not for nonparticipants (Wood et al. 1989).

The evidence that reduced absenteeism follows cessation complements findings based on comparisons of current smokers with nonsmokers. The reduced rate after cessation supports a causal interpretation, rather than attributing the association to an indirect pathway or to confounding factors.

In summary, there is consistent evidence demonstrating that employees who are current smokers have a greater likelihood of absences from work compared with employees who have never smoked. Additional evidence is needed on dose-response trends and, more importantly, on changes in absence rates before and after smoking cessation. Other reviewers have concluded that reduced absenteeism could lead to potential savings that can be accrued from smoking cessation programs in the workplace (Kristein 1983; Warner et al. 1998).

Medical Services Utilization

Medical services utilization provides another measure of the global effects of smoking on health. The *most important utilization indicators in studies on* smoking can be grouped into three general categories: (1) costs, (2) outpatient visit rates, and (3) hospitalization rates. Interpreting these findings requires consideration of the many factors influencing medical services utilization. Smokers, for example, are less likely than nonsmokers to use preventive services such as screening (Beaulieu et al. 1996; Edwards and Bouler 1997). However, the high incidence of smoking-induced diseases among smokers will tend to drive their medical care needs. The socioeconomic and educational differences between smokers and nonsmokers also complicate data interpretation because of potential confounding. Comparisons of smokers within well-defined groups, such as particular workforces or health care plans, should provide unbiased comparisons.

Costs

In evaluating the relationship between smoking and medical care costs, only those studies directly addressing expenditures were considered (Table 6.8). The literature on comparative lifetime costs of medical care for smokers and nonsmokers based on assumed models and projections was not considered relevant to this chapter. Of the seven studies reviewed, six showed the medical costs of smokers to be greater by at least 15 percent in at least one subgroup. In one study of enrollees in a health maintenance organization, smokers had costs 25 percent higher than nonsmokers among those younger than 65 years of age, but few differences were observed in those age 65 years or older (Terry et al. 1996). Only the study by Vogt and Schweitzer (1986) on enrollees in Kaiser Permanente found no differences between smokers and nonsmokers.

Two studies not included in Table 6.8 are also relevant. In a population of retirees followed for one year, smoking was associated with added health care costs of more than $1,300 per year per pack of cigarettes smoked per day, after adjusting for age, gender, education, seat belt use, and alcohol consumption (Leigh and Fries 1992). In a study conducted as part of a worksite health promotion program in Birmingham, Alabama, smokers were found to have incurred more costs than nonsmokers, but the data were not presented (Weaver et al. 1998).

Outpatient Services

In several studies (Table 6.8), smokers were at least 15 percent more likely than nonsmokers to use outpatient services (Peters and Ferris 1967; Palmore 1970; Chetwynd and Rayner 1986; Freeborn et al. 1990);

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one study found an increased likelihood of 6 percent (Rice et al. 1986). In studies that stratified age and gender, strong associations with smoking were observed in particular groups. Male smokers were more frequent users of outpatient services than were male nonsmokers, but this difference was not found among females in one study (Oakes et al. 1974). In another study, this gender difference occurred in young but not old persons (Ashford 1973). Three studies showed only small differences in the use of outpatient services between smokers and nonsmokers (Vogt and Schweitzer 1985; Halpern and Warner 1994; Miller et al. 1999).

The frequency of outpatient visits does not appear to increase with the number of cigarettes smoked (Peters and Ferris 1967, Balarajan et al. 1985; Marsden et al. 1988). However, regardless of the number of cigarettes smoked, some studies documented a large difference in the number of visits by smokers compared with nonsmokers.

Hospitalization

In all but one of the studies considered (Terry et al. 1999), smokers had higher hospitalization rates than nonsmokers; the differences were at least 10 percent. In two other studies that stratified age and gender, one study found an association in males but not in females (Oakes et al. 1974), and the other study found an association only among younger females (Ashford 1973).

Additional studies corroborate the results summarized in Table 6.8. In a study of a cohort of retirees followed for one year, the number of packs of cigarettes smoked per day was significantly associated with the number of days hospitalized (Leigh and Fries 1992). In a study of 1,000 veterans accessing the Veterans Administration system in Connecticut, tobacco users were significantly more likely ($p < 0.01$) than nonusers to be hospitalized, and tobacco users were significantly more likely ($p < 0.01$) than nonusers to be hospitalized and to spend more days in the hospital (Benedetto et al. 1998). In a study of Kaiser Permanente enrollees in Oregon, Pope (1982) observed a weak, nonsignificant correlation between a smoking index and hospitalization rates in the youngest age group for men and women (aged <35 years), but this association was not present in the other age groups studied.

Dose-response data are available from two prospective cohort studies (Table 6.9). In the Coronary Drug Project, the five-year hospitalization rates for smokers compared with nonsmokers plateaued at the lowest smoking category, and were more compatible with a threshold relationship than with a nonthreshold dose-response relationship. However, it was unclear whether these analyses accounted for the higher mortality rates experienced by smokers relative to nonsmokers during the follow-up period (Coronary Drug Project Research Group 1976). In a two-year follow-up of smokers in the American Cancer Society Cancer Prevention Study I (CPS-I) a strong dose-response relationship was present: compared with those who smoked 1 to 9 cigarettes per day, those who smoked 10 to 19, 20 to 39, and 40 or more cigarettes per day had an increased likelihood of hospitalization during the follow-up period of 8.5 percent, 14.6 percent, and 28.0 percent, respectively (Hammond 1965). In a cross-sectional survey of U.S. military personnel that compared smokers with nonsmokers, those who smoked one-half of a pack or less, one pack, and one and one-half packs or more per day had increases in self-reported days hospitalized of 28.1 percent, 6.3 percent, and 54.7 percent, respectively (Marsden et al. 1988).

Former Smokers

Studies comparing the use of medical services by former smokers with lifetime nonsmokers are summarized in Table 6.10. Costs were 26 percent higher for former smokers in one study (Pronk et al. 1999), and higher for some services but not higher overall in another study (Vogt and Schweitzer 1985). In every study, former smokers were more likely than lifetime nonsmokers to use outpatient services. In a study conducted in the United Kingdom that was stratified by age and gender, smokers were more likely than nonsmokers to have general practice health care providers visit their homes for an illness (Ashford 1973). The use of outpatient services by smokers remained elevated compared with that of nonsmokers long after smoking cessation (Halpern and Warner 1994). For hospitalizations the findings were mixed, with three studies showing higher rates in former smokers (Van Peenen et al. 1986; Kaplan et al. 1992; Halpern and Warner 1994). In one of these studies, however, the difference was eliminated after adjusting for age, and in two other studies there were only small differences between former smokers and lifetime nonsmokers. In another study that stratified age and gender, former smokers were more likely than lifetime nonsmokers to be hospitalized in some strata, but less likely in others, without a consistent pattern (Ashford 1973).

These studies generally have not taken into account prior smoking history and time since quitting, nor have they considered whether development of a

Table 6.7 Studies on the association between former smoking and absenteeism

Study	Population	Group
Holcomb and Meigs 1972	226 male factory employees	Total
Wilson 1978	1970 National Health Interview Survey; persons aged 17 years	[illegible] Men Women 17–44 years 45–64 years 65 years
U.S. Department of Health and Human Services 1990	Nationally representative population sampling of 42 states, United States	1965 Men Women 1977 Men Women
Jenzon et al. 1981	1,001 Swedish men aged 47–48 years	Total
Gallo 1983	152 [illegible] industrial occupational employees	[illegible] current smoker = 52 Ex-smoker = [illegible]
Jacobson et al. 1989	10-year follow-up of 5,000 [illegible] former servicemen, including Navy, California police officials, and Kaiser employees	[illegible] Current smoker Ex-smoker, recent quitter Ex-smoker, previous quitter Lifetime nonsmoker Current smoker: 2 yrs 5 yrs

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
Total days lost per person per year			
6.37	4.42	44.1	Short-term: <7 days unverified medical absences
Absence rate: short-term			Long-term: ≥10 days verified medical absences
0.75	0.38	97.4	
Absence rate: long-term			
0.10	0.07	42.9	
Mean workdays lost per year			None
5.2	3.4	52.9	
5.1	3.5	45.7	
5.4	3.7	45.9	
4.3	2.8	53.6	
5.7	3.3	72.7	
9.6	4.8	100.0	
Workdays lost per year due to illness and injury per currently employed persons			None
6.8	4.6	47.8	
6.7	4.8	39.6	
6.1	4.2	45.2	
5.4	3.7	45.9	
Persons reporting [illegible] during the past year			None
1	1	0.0	
Mean [illegible]			Based on [illegible] self-report questionnaire
4.7	4.[illegible]	[illegible]	
0.[illegible]	[illegible]	[illegible]	
Annual [illegible]			Ranked comparisons of [illegible] days for [illegible]
[illegible]	[illegible]	[illegible]	[illegible]
5.9	3.6	[illegible]	
5.0	3.8	[illegible]	
5.8	3.6	[illegible]	
5.3	3.2	[illegible]	
4.8	3.2	[illegible]	
4.1	2.6	57.7	
4.4	2.6	69.2	

Table 6.7 Continued

Study	Population	Group
Manning et al. 1989	324 employees of 2 companies, aged 20–75 years	Baseline Short term absences Recent quitters Sustained quitters Long-term absences Recent quitters Sustained quitters 1-year follow-up Short-term absences Recent quitters Sustained quitters Long-term absences Recent quitters Sustained quitters
Lowe and Mitchell 1981	16-year Framingham study, persons age 30–62 years	[illegible] Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey (nationally representative sample)	Time since cessation Never smoked 1–2 years 3–4 years 5–10 years 11–15 years >20 years
Postma et al. 1994	402 workers of several [illegible] ages 18 years (clerks) and 41 years (shop [illegible] Netherlands	Clerks Shop [illegible]
Bush and Wooden 1995	1989 Australian National Health Survey, n = 21,984 employed persons from randomly selected households	Men: 1.[illegible] Women: 0.145

*OR = Odds ratio.

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Results			
Former smokers	Nonsmokers	Percentage difference	Comments
Mean hours absent per month			Short-term: ≤2 days Long-term: >2 days Sustained: >1 year Recent: ≤1 year
2.21	1.69	30.8	
1.47	1.69	-13.0	
1.35	0.78	76.9	
0.88	0.78	-12.8	
2.21	1.17	88.9	
1.15	1.17	-1.7	
1.90	1.67	13.8	
[illegible]	1.67	16.8	
Mean annual absence episodes during the year			None
4.9	6.1	-20.0	
Mean annual [illegible] episodes			
1.8	[illegible]	0	
Total days absent			
0.1	0.2	-25.0	
Work loss days during past 2 weeks			ORs*
2.61	1.0	161.0	
1.45	1.0	45.0	
1.46	1.0	17.6	
1.2	1.0	0.0	
1.41	1.0	41.0	
1.28	1.0	28.0	
Activity prevalence			
0.74	1.0	25.0	OR
1.25	1.0	25.0	OR
Any absence 2 weeks before the survey			OR was adjusted for demographics (age, gender, ethnicity, marital status, education, location of residence, job characteristics (employment status, hours worked, income, occupation, industry), and health risk factors (alcohol use, physical exercise, body weight); additional factors measured overall health and happiness (more specific information was not provided)
1.33	1.0	33.0	
1.19	1.0	19.0	

admitted to the hospital more often. Among patients admitted to the hospital, smokers have longer lengths of stay and incur greater expenses per admission than nonsmokers. Less information is available concerning the use of medical services such as prescription drugs and emergency department visits, but increases for smokers compared with nonsmokers have also been observed with respect to these outcomes (Chenoweth and Reyner 1986; Miller et al. 1998). Although smokers use more palliative care services, as demonstrated by this review, smokers have been less likely than nonsmokers to use preventive services such as multiphasic testing (Oakes et al. 1974) and screening (Beaulieu et al. 1996; Edwards and Boulet 1997).

Postoperative Complications

In comparison with nonsmokers, smokers have been hypothesized to be at a higher risk for postoperative complications because of a greater frequency of chronic diseases, impaired pulmonary reserve, altered immune responses, and impaired wound healing. Higher rates of postoperative complications in smokers could contribute to the greater costs that they incur for health care services.

Substantial clinical and experimental research has been conducted on the relevant effects of smoking on host defenses, immune responses, and wound healing. As reviewed elsewhere in this report and in a previous Surgeon General's report (USDHHS 1990), smoking produces a range of effects on respiratory defense mechanisms that may increase the risk for postoperative pneumonia. Compromised lung function and the presence of COPD increase the risks for respiratory complications, including respiratory failure. The increased likelihood of coronary heart disease (CHD) in smokers increases the risk for cardiac events during and after surgery. In animal and clinical models, exposure to tobacco smoke and nicotine specifically impaired aspects of wound healing (Brown et al. 1986; Silcox et al. 1985; Haverstock and Mandracchia 1998; Jorgensen et al. 1998; Hollinger et al. 1999).

The literature on postoperative complications is extensive and diverse in the scope of complications associated with smoking. Table 6.11 provides evidence for lower survival rates after surgery for smokers compared with nonsmokers and suggests that this increased mortality may reflect a range of specific and nonspecific consequences of smoking, including a greater risk for postoperative complications related to the surgery. A number of reports address specific surgical complications such as flap failures, wound infections, and poor orthopedic outcomes. A similarly diverse set of reports consistently shows that smoking also increases the risk of respiratory complications.

Table 6.7 Continued

Study	Population	Group
Wooden and Bush 1995	4,812 randomly sampled former smokers, Australian National Health Survey	Test of Time since cessation 1–4 years 5–9 years 10–19 years ≥20 years
[illegible] et al. 1998*	5,963 men (aged 40–64 years, at [illegible] 3,490 women (aged 55–59 years), [illegible]	Men Women
[illegible]	[illegible]	Men Women

disease led to quitting. The extent of smoking before quitting is a determinant of risk, and risks fall for many diseases as the duration of quitting lengthens. The somewhat inconsistent findings may reflect (1) the heterogeneity of former smokers in these studies and (2) analysis strategies that did not fully account for risk determinants in the former smokers. In an analysis of the 1990 National Health Interview Survey data that accounted for time since quitting, former smokers had significantly more hospital admissions until 10 years following cessation, at which point former smokers and lifetime nonsmokers had similar numbers of hospital admissions (Halpern and Warner 1994).

The clinical trials of Wagner and colleagues (1995) provide additional evidence. Two cessation trials followed participants and collected medical care utilization data. After six years of follow-up, quitters experienced reductions in outpatient visits, hospital admissions, and hospital days in both trials compared with persistent smokers. In contrast, medical care utilization continued to increase among persistent smokers: 7 to 15 percent for outpatient visits, 30 to 45 percent for hospital admissions, and 75 to 100 percent for days spent in the hospital. These divergent patterns in the use of medical care services resulted in substantially greater rates of hospitalization, hospital days, and outpatient visits for persistent smokers.

Age

Several studies suggest that smoking may have a greater impact on the youngest age groups compared with older age groups. More frequent use of outpatient (Peters and Ferris 1967; Newcomb and Bentler 1987) and inpatient (Newcomb and Bentler 1987) services among smokers than among nonsmokers has been observed even in adolescents and young adults, suggesting that the differences observed in smoking and nonsmoking older adults are not solely a result of smoking-induced diseases. In fact, in a few studies higher levels of service utilization were observed among smokers than among nonsmokers in the younger age groups, but such differences were either not present or were reversed in the oldest age groups. This pattern is evident in the cross-sectional analyses of the 1970 U.S. National Health Interview Survey data, a random sample of U.S. households in which both smoking men and smoking women had a markedly higher number of days hospitalized per year than their nonsmoking counterparts until they reached their mid-40s, at which point the differences between smokers and nonsmokers became more subtle (Weinkam et al. 1987).

In general, compared with nonsmokers, smokers tend to incur more medical costs, to see physicians more often in the outpatient setting, and to be

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
ORs for incidence of absence during past 2 weeks (modeled)			Adjusted for several potential confounders
1.04	1.0	4.0	
0.53			
0.50			
0.32			
0.22			
Periods of absence			Adjusted reduction
1.10	1.0	10.0	
1.03	1.0	3.0	
Days absent			
1.06	1.0	6.0	
1.03	1.0	3.0	

Table 6.8 Studies on the association between current smoking and medical service costs

Study	Population	Group
	Costs	
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
[illegible] et al. 1981	[illegible] HMO enrollees aged 18–[illegible]	Group I (1969–1974) Group II (1970–1976)
[illegible] and [illegible] 1990	2,963 employees and [illegible] [illegible] health service plans	Male Average cost per observation Standard deviation of cost per day
[illegible] et al. 1998	U.S. Panel on Health Effects of [illegible] Smoking, ages ranging [illegible] years	Men Women
Candelaria et al. 1995	12,881 [illegible] health plan [illegible] 2 [illegible] [illegible] [illegible] [illegible] 1993–1994 [illegible]	[illegible]
Jones et al. 1994	9,906 HMO enrollees aged [illegible] years	Aged 18–64 years Aged 65 years
[illegible] et al. 1994	[illegible] Oral Health [illegible] Minnesota	Total
	Hospital services	
Peters and Ferris 1967	Health Interview Survey	Total
Feldman 1970	2,68 [illegible] subscribers aged 60–84 years at baseline	Total

*HMO = Health maintenance organization.
†NR = Data were not reported.

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
$18,515	$19,772	-6.4	None
12,412	11,958	3.8	
6,819	6,923	-1.5	
97,771	83,328	0.7	
[illegible]	[illegible]	[illegible]	Average ambulatory care costs
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	None
[illegible]	[illegible]	[illegible]	
$15,514	$27,275	[illegible]	None
12,562	22,783	23.7	
$27,262	$ [illegible]	[illegible]	Average excess cost over 4 years
$ [illegible]	$ [illegible]	9.2	Charges per month
[illegible]	208	1.2	
748	508	19.1	Absolute values were not reported. Adjusted for age, race, marital status, body mass index, physical activity, and comorbidity conditions
[illegible]	[illegible]	[illegible]	Clinic visits, Harvard 1961–1965
32.0	26.0	20.6	Percentage with 0 medical visits per year. Comparisons with present use of tobacco vs. subjects who did not use tobacco. Definitions: present use of tobacco, nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, ≤2 cigars and/or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and/or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as ≥11 cigarettes per day, ≥5 cigars and/or pipes per day, constant use of snuff, or constant use of chewing tobacco

Table 6.8 Continued

Study	Population	Group
	Outpatient services	
Ashford 1973	32,310 residents of Exeter, United Kingdom, aged ≥15 years	Home visits Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years Hospital outpatient Men: 15–29 years 30–44 years 45–59 years ≥60 years Women: 15–29 years 30–44 years 45–59 years ≥60 years
Oakes et al. 1974	2,557 HMO enrollees, aged ≥20 years	Men: Total 20–34 years 35–49 years ≥50 years Women: Total 20–34 years 35–49 years ≥50 years
Regional Health Authority 1985	2,482 adult HMO enrollees	Total
Chesswood and Rayner 1986	808 women, aged 18–65 years	Clinic [illegible] Number of consultations 0 1–4 5–9
Rice et al. 1986	1979 National Health Interview Survey participants	Total Age Age Age
Beresford et al. 1987	2,013 HMO enrollees aged ≥65 years	Total Total

Results			
Smokers	Nonsmokers	Percentage difference	Comments
			Number of visits during the survey year
0.21	0.17	23.5	
0.28	0.18	55.6	
0.43	0.33	30.3	
1.4	2.3	-39.1	
1.3	1.1	18.2	
0.67	0.84	4.7	
0.44	0.49	-10.2	
2.1	2.2	-4.5	
0.62	0.45	37.8	
0.47	[illegible]	23.2	
0.7	0.45	[illegible]	
0.46	0.57	[illegible]	
0.56	0.46	21.7	
0.5	0.47	[illegible]	
0.65	0.52	[illegible]	
0.43	0.55	[illegible]	
3.4	2.8	21.4	Mean number of office visits during the past year
[illegible]	5.4	25.2	
3.2	2.4	33.3	
[illegible]	5.0	[illegible]	
4.2	4.8	[illegible]	
5.5	5.4	[illegible]	
3.0	4.0	-12.5	
1.1	2.0	-45.0	
[illegible]	3.667	[illegible]	Total office visits
[illegible]	2.95	25.1	Students — non-smokers
3.71	4.50	[illegible]	
0.52	0.43	91.1	
[illegible]	0.84	25.0	
[illegible]	11.7	33.3	
5.2	[illegible]	[illegible]	Physician visits in past year per year
4.2	[illegible]	[illegible]	
5.3	[illegible]	[illegible]	
7.0	[illegible]	[illegible]	
[illegible]	9.35	9.9	Office visits per year
6.6	6.50	0.6	

Table 6.8 Continued

Study	Population	Group
	Outpatient services	
Halpern and Warner 1994	1969 [illegible] National Health Interview Survey	Total
Mechanic 1969	1964 National Medical Expenditure Survey, n = 38,846	Total
	Hospitalizations/inpatient services	
Palmore 1970	268 community volunteers, aged 60–94 years at baseline	Total
Ashford 1973	[illegible], United Kingdom, aged ≥15 years	Men: [illegible] 30–44 years 45–59 years ≥60 years Women: [illegible] 30–44 years 45–59 years ≥60 years
Oakes et al. 1974	2,557 HMO enrollees, aged ≥20 years	Men: [illegible] 40–59 years ≥60 years Women: 20–39 years 40–59 years ≥60 years
Coronary Drug Project Research Group 1975	2,789 men with a history of myocardial infarction, aged 30–64 years at baseline	Total

*OR = Odds ratio.

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
1.01	1.00	1.0	Physician visits in the past year; OR[1]
[illegible]	[illegible]	[illegible]	[illegible]
38.0	33.0	15.2	Percentage with ≥1 operation; nonsmokers/slight present use of tobacco vs. moderate present use/heavy present use of tobacco; nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, 1–2 cigars and/or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and/or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as ≥11 cigarettes per day, ≥5 cigars and/or pipes per day, constant use of snuff, or constant use of chewing tobacco
[illegible]	[illegible]	[illegible]	Average [illegible] days hospitalized during the survey year
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

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Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	Comments
Not applicable	Referent	8.5	14.6	None
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0	[illegible]	[illegible]	54.7	[illegible]
[illegible]	23.9	21.[illegible]	38.5	[illegible]
0	46.9	46.[illegible]	43.8	None
0	[illegible]	[illegible]	9.8	
[illegible]	[illegible]	6.[illegible]	8	Number of cigarettes per day in the past year

of health status held by current smokers was significant[illegible], lower than that held by nonsmokers (Erikson 1986). In a multiple regression analysis of data collected from approximately 18,000 men and women in Finland, which included variables for sociodemographic characteristics, family life, morbid conditions, pain, psychosocial problems, and relative weight, smoking was associated with a significantly lower perceived health status in men but not in women (Fylkesnes and Forde 1991). In a random sample of 1,200 adults in South Wales, United Kingdom, the mean score on the SF-36 general health perception scale among participants who had ever smoked was 7.8 points lower than for those who had never smoked (Lyons et al. 1994). A study using the same scale with 921 U.S. male military veterans showed that current smoking was significantly inversely correlated with good general health perceptions (Schnurr and Spiro 1999). In a telephone survey of Newfoundland residents, the likelihood of rating one's health as good declined in proportion to the number of cigarettes smoked per day; those who had never smoked were more than four times more likely than smokers of more than 30 cigarettes per day to rate their health as good (Segovia et al. 1989). In a survey of 1,625 patients from nine medical practices in Scotland who had a history of smoking, persistent smokers rated their general health 8.0 percent lower than former smokers rated theirs on the SF-36 scale (Tillmann and Silnick 1997). Among 2,502 enrollees in an Oregon health maintenance organization, smoking was negatively correlated with general health status for both men and women, an observation that extended to measures of mental and physical health status (Pope 1982).

Smokers in at least one subgroup were at least 10 percent more likely than nonsmokers to rate their health as poor, including studies that compared self-reported chronic conditions (Balarajan et al. 1985;

Table 6.10 Studies on the association between former smoking and medical services utilization costs and rates

Study	Population	Group
	Costs	
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
Fronk et al. 1969	[illegible] HMO enrollees, Minnesota	[illegible]
	Outpatient services	
Peter[illegible] 1967	Harvard, Radcliffe [illegible]	[illegible]
Ashton 1972	32,210 residents of Leeds, United Kingdom aged [illegible] years	Hospital costs: Men: [illegible] years 35–44 years 45–59 years ≥60 years Women: [illegible] years 35–44 years 45–59 years ≥60 years Hospital patients: Men: [illegible] years 35–44 years 45–59 years ≥60 years Women: [illegible] years 35–44 years
Oakes et al. 1974	2,557 HMO enrollees aged ≥20 years	Men: Total 20–39 years 40–59 years ≥60 years Women: Total 20–39 years 40–59 years ≥60 years

*HMO = Health maintenance organization.
†NR = Data were not reported.

Former smokers	Nonsmokers	Percentage difference	Comments
Results			
$21,150	$19,772	7.0	None
13,619	1,958	12.2	
8,833	[illegible]	24.8	
94,754	[illegible]	1.9	
NR†	NR†	[illegible]	Procedures were categorized as hysterectomy, tonsillectomy, and appendectomy; [illegible]
[illegible]	[illegible]	[illegible]	[illegible] Hammond 1964, 1966
[illegible]	[illegible]	[illegible]	Number of visits during the survey year
0.26	[illegible]	[illegible]	
[illegible]	0.18	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	2.5	[illegible]	
[illegible]	1.1	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	2.3	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	2.8	[illegible]	Mean number of office visits during the past year
[illegible]	2.4	[illegible]	
[illegible]	2.4	20.9	
4.3	3.9	10.3	
5.9	4.8	22.9	
5.1	5.4	-5.8	
7.4	4.0	85.0	
5.0	5.0	0.0	

Table 6.10 Continued

Study	Population	Group
	Outpatient services	
Balarajan et al. 1985	1980 General Household Survey, United Kingdom	Outpatient visits Stopped ≥1 year Stopped <1 year Hospitalizations with a physician Stopped ≥1 year Stopped <1 year
[illegible] Schweitzer 1985	2,582 adult HMO enrollees	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit [illegible] Quit 2 years to [illegible] Quit 1 year Quit 2 to [illegible] Quit 11–[illegible] Quit ≥20 years
	Hospitalizations/inpatient services	
Ashton 1972	32,210 residents of Leeds, United Kingdom aged ≥15 years	Men: [illegible] years 35–44 years 45–59 years ≥60 years Women: [illegible] years 35–44 years 45–59 years ≥60 years
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Van Peenen et al. 1985	[illegible]	Total
Seljeflot et al. 1986	681 residents of a southern Norwegian community, aged >65 years	Total

†OR = Odds ratio.

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Results			
Former smokers	Nonsmokers	Percentage difference	Comments
1.40	1.0	40.0	OR for prevalence of chronic illness after adjustment for age, gender, and socioeconomic group
1.25	1.0	25.0	
1.19	1.0	19.0	
1.47	1.0	47.0	
[illegible]	[illegible]	12.9	Tests of [illegible]
1.20	1.0	20.0	OR for the [illegible]
1.47	1.0	47.0	
1.32	1.0	32.0	
1.24	1.0	24.0	
1.25	1.0	25.0	
1.18	1.0	18.0	
[illegible]	[illegible]	[illegible]	Average number of days [illegible] during the year
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	Number of hospital days
[illegible]	[illegible]	[illegible]	Time was not different after adjusting for age
4.0	3.1	28.6	Annual [illegible] rates of hospitalization in the [illegible] study

Table 6.10 Continued

Study	Population	Group
	Hospitalizations/inpatient services	
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit 0–2 months Quit 3 months–1 year Quit 2–4 years Quit 5–10 years Quit 11–19 years Quit ≥20 years
[illegible]	[illegible]	Age of quit Age 6[illegible] years

Halpern and Warner 1994), acute conditions (Balarajan et al. 1985), and physical symptoms (Macnee 1991; York and Hirsh 1995). An increasing number of cigarettes smoked per day was consistently associated with increased risks for symptoms or illnesses (Balarajan et al. 1985; Marsden et al. 1988; Joung et al. 1995), and with a greater likelihood of rating one's health as poor (Joung et al. 1995; Poikolainen et al. 1996; Manderbacka et al. 1998) (Table 6.13), with differences between the highest and lowest exposure categories of about 30 percent or greater in every study that assessed dose-response trends (Table 6.13). For several measures of poor health, the differences between former smokers and lifetime nonsmokers (Table 6.14) tended to be even more striking than for comparisons between current smokers and lifetime nonsmokers, probably because of the increased likelihood of quitting among those experiencing symptoms or diagnosed with illnesses.

A few studies examined reports of fatigue or tiredness. In a survey of New Zealand women who worked at home, smokers were 71 percent more likely than nonsmokers to report frequently feeling tired for no reason (Chetwynd and Rayner 1988). In a study of retired persons in the United States, after adjusting for age, current smokers were 60 percent more likely than lifetime nonsmokers to report becoming very tired easily (Rimer et al. 1990); former smokers were 25 percent more likely than lifetime nonsmokers to report getting very tired easily (Rimer et al. 1990).

Smokers tend to rate their general level of well-being lower than do nonsmokers whether well-being is measured directly (Dennerstein et al. 1994), assessed overall as quality of life (Sippel et al. 1999), or rated by degrees of general satisfaction with life (Blair et al. 1980) (Table 6.12). Similar findings have been observed when former smokers were compared with lifetime nonsmokers (Table 6.14) (Blair et al. 1980; Sippel et al. 1999). Conversely, compared with lifetime nonsmokers, current smokers tend to rate themselves as more dissatisfied with life (Table 6.12) (Kaprio and Koskenvuo 1988), but few differences in the prevalence rates of life dissatisfaction were observed between former smokers and nonsmokers (Table 6.14) (Kaprio and Koskenvuo 1988).

With respect to mental health and well-being, smokers tend to rate themselves slightly lower on measures of mental health or mental well-being (Wakefield et al. 1995; Wooden and Bush 1995; Sippel et al. 1999). In addition, smokers are more likely than nonsmokers to have psychological symptoms such as depressed mood and phobic anxiety (Matarazzo and Saslow 1960; Macnee 1991; Schoenborn and Horm 1993). In the South Wales study, not included in the summary tables, current smokers had a mean SF-36 mental health score that was slightly but not significantly lower than that of people who had never smoked (Lyons et al. 1994). Former smokers also tend to rate themselves less favorably than do nonsmokers

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
1.79	1.0	79.0	ORs for hospital admissions
2.59	1.0	159.0	
1.25	1.0	25.0	
1.32	1.0	32.0	
1.04	1.0	4.0	
1.0	1.0	-3.0	
[illegible]	[illegible]	[illegible]	Percentage with [illegible]
[illegible]	[illegible]	[illegible]	

(Table 6.14). The differences between former smokers and lifetime nonsmokers were small with respect to mental health and well-being (Wetzler and Ursano 1988; Wooden and Bush 1995; Sippel et al. 1999), but were more marked on measures of symptoms or morbidity (Table 6.14) (Lilienfeld 1959; Lindenthal et al. 1972; Macnee 1991). A strong dose-response trend was observed between smoking frequency and depressed moods in nationally representative U.S. data from the National Health Interview Survey (Schoenborn and Horm 1993). However, dose response trends generally did not occur for mental health measures (Table 6.13) (Lindenthal et al. 1972; Wetzler and Ursano 1988; Stangfeld et al. 1993).

Studies of physical functioning, or functional status, among elderly populations also provide relevant evidence. Although they are not a focus of this review, such studies have provided prospective evidence that cigarette smoking is associated with accelerated declines in physical function (Pinsky et al. 1987; Guralnik and Kaplan 1989; Berkman et al. 1993; Strawbridge 1993). An analysis of data from the Honolulu Heart Study showed that smoking was inversely associated with freedom from clinical illnesses, physical impairment, and cognitive impairment (Reed et al. 1998).

The evidence provides a clear indication that smokers perceive their health as poorer than nonsmokers perceive theirs. Smokers report more symptoms (including mental health symptoms) and illness episodes, feel more tired, and have lower ratings for physical health status. Compared with nonsmokers, smokers even report lower overall levels of well-being for reasons that may at least partially reflect their diminished health status. The consistent indications of a poorer health status among smokers compared with nonsmokers across numerous health status dimensions provide direct evidence that smoking is associated with a diminished health status.

Evidence Synthesis

This section reviewed evidence on smoking and a diverse but interrelated set of measures of health status. Although the measures are nonspecific and likely to be affected by factors other than smoking, there is abundant and consistent evidence that smokers generally have a poorer health status than nonsmokers. This section reviewed findings on self-reported health statuses, absenteeism, and medical services utilization rates, as well as complications of surgical care. For each of these outcomes, the weight of the evidence indicates an adverse effect from smoking. There are many studies with differing designs and a variety of populations. The strength of the association with smoking is variable across the outcome measures and across study

Table 6.11 Studies on the association between smoking and complications of surgery

Study	Population	Outcome studied
	Postoperative and wound-healing complications	
Abidi et al. 1998	Retrospective study, 83 c[illegible] ve patients with fractures of the calca[illegible] who underwent open reduction and internal fixation during a 3-year period	Postoperative and wound complications
Ger[illegible] et al. 1998	[illegible]	Operative procedure and outcome
Goo[illegible] et al. 1999	[illegible] ubclavian-carotid bypass [illegible] between 1992 and 1997	Adverse cardiac and pulmonary events
Sp[illegible] et al. 2000	681 patients undergoing CABG between December 1, 1996 and November 30, 1997	Surgical wound infection, dose-related and post-operative bacteremia
	Postoperative complications	
Ash[illegible] et al. [illegible]	43 consecutive patients who underwent cardiovascular surgery	Mortality
Wa[illegible] et al. 1[illegible]	500 women who had cancer of the [illegible] who were consecutive patients [illegible] Hospital, [illegible] between 1985 and 1990	Postoperative complications
D'Ag[illegible] et al. 1996	Prospective cohort study of patients undergoing first-time isolated, non-emergency coronary artery bypass grafting between January 1, 1991 and December 31, 1993 in Northern New England	Perioperative risk of stroke
Kh[illegible] et al. 1[illegible]	854 consecutive free flaps	Successful outcome
Samuels et al. 1998	All patients aged ≥40 years who had a diagnosis of [illegible] [illegible] Hospital in Pennsylvania [illegible] 1, 1[illegible] June 1995	Postoperative cardiac arrest
Udey et al. 1998	Prospective [illegible] history of CABG	Perioperative [illegible] complications

[illegible] = Coronary artery bypass graft

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Results

A history of active smoking was correlated with an increase in time to heal the wound in the outpatient group. Risk factors for wound complications: high body mass index, extended time between injury and surgery, smoking, and single-layer wound closure

[illegible]

[illegible]

[illegible]

Source: https://www.industrydocuments.ucsf.edu/docs/skmj0001

Results

Complications occurred in 22% of current smokers, 13.8% of former smokers, and 4.9% of nonsmokers (adjusted OR = [illegible] (1.9–16.2) for current smokers vs. nonsmokers, 4.2 (95% CI, 1.2–14.8) for former smokers, [illegible] for current smokers who reduced their smoking 1 month before surgery = 6.7 (95% CI, 2.5–17.1)).

The number of [illegible] complications, surgical site infections, [illegible] smoking habits, inflammatory bowel disease, maternal [illegible] smokers [illegible] patient-ship status.

[illegible] overall risk of developing [illegible] packs/day).

[illegible] patients who had complications (smokers = 23%, former smokers = 17%, and nonsmokers = 7%; p < 0.001). After [illegible] smoking [illegible] smokers. Former smokers had a significantly [illegible] nonsmokers.

Smokers [illegible] surgical [illegible] surgical [illegible] longer [illegible] smokers but [illegible] smokers.

Postoperative [illegible] presence of chronic [illegible] surgery duration [illegible] p < 0.01).

Smoking was [illegible] complications [illegible] (OR = [illegible] 95% CI, 1.1–10.7; p < 0.05).

Pack-years of smoking, age, [illegible] and current smoking status were [illegible] predictors of airway obstruction/bronchospasm (OR = [illegible] 95% CI, 1.2–38.4); pack-years of smoking were not associated with the need for endotracheal intubation (OR = 1.1 [95% CI, 0.4–3.2]) or with prolonged intensive care or readmission.

Table 6.11 Continued

Study	Population	Outcome studied
	Postoperative complications	
Chan et al. 2000	67 consecutive patients (84% smokers) who underwent surgical resection of [illegible] esophageal carcinoma from January 1989 to December [illegible]	5-year survival rate
Chandrasekaran and Sweeney 2000	567 consecutive patients [illegible] (40% nonsmokers, including 7% ex-smokers and 53% smokers), undergoing [illegible] major elective surgery, who had standard anesthetic, perioperative [illegible]	Postoperative [illegible] and [illegible]
Kotani et al. 2000	[illegible] smoking and [illegible] who had [illegible] hepatic [illegible] surgery [illegible] in Japan	[illegible] and [illegible] macroscopic [illegible]
Westerdahl et al. 2000	Healthy [illegible] coronary [illegible] who had [illegible] coronary artery bypass [illegible]	[illegible] [illegible] [illegible]
	Wound-healing complications	
Carrillo et al. 1968	[illegible]	Wound infection
Erdmann et al. 1990	[illegible]	Wound healing
Takeishi et al. 1997	114 patients who had transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction in Japan	Wound healing complications

populations, probably reflecting the nonspecificity of these measures and the differing mixes of parental confounding and modifying factors across studies. In general, there is evidence for an increasing severity of outcome measures with an increasing number of cigarettes smoked, and current smokers tend to have worse outcomes than former smokers. Studies have addressed potential confounding factors to a limited extent, depending on the availability of data on relevant factors. Given the diversity of populations, study designs, and consistency of findings, confounding alone does not seem to be a satisfactory explanation for the overall pattern of findings. A single, unifying biologic basis for the association of smoking with the outcome measures cannot be postulated, but there are many well-supported direct and indirect mechanisms that may link smoking to the adverse effects documented in this section.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

Results

Poor outcomes (18% survival rate) mainly because most tumors were in advanced stages when resected.

6% of smokers compared with 15% of [illegible] were alive [illegible] (p < 0.05).

Smoking was associated with macrophage [illegible] microbicidal activity.

Smoking ≥20 packs [illegible] <20 pack-years (p = 0.04).

Heavy smoking [illegible] (p = 0.04).

Peripheral vascular disease and heavy alcohol use were confirmatory factors in subjects not healing.

Smoking was associated with a greater risk (p = 0.03).

2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Implications

Although preventing the specific diseases caused by smoking has been a public health priority for a long time, cigarette smoking also causes a substantial and costly burden of nonspecific morbidity. Smokers have a poorer health status, lose more time from work, and use medical care services at a higher rate than their nonsmoking peers. These adverse effects occur among younger smokers even before the burden of smoking-induced diseases becomes apparent at middle age and older.

Table 6.12 Studies comparing the health status of smokers and nonsmokers

Study	Population	Group
	Mean number of illness episodes during the past year	
Chetwynd and Rayner 1988	Survey of 978 women who worked at home, Christchurch, New Zealand, aged 18–60 years	Total Aged 18–29 years Aged 30–44 years Aged 45–60 years
	Self-reported chronic conditions	
Haapanen and Wanner 1994	[illegible] Health Interview Survey, random sample [illegible] aged ≥ [illegible]	Total
	Physical symptoms (5 categories)	
Macnee 1991	241 men and [illegible] years, mean age [illegible] years	Total
	Physical symptoms (10 symptoms)	
York and Strobl 1995	[illegible] Current, ex-drinkers, and [illegible] drinkers, aged 20–[illegible] years	Current drinkers Men Women Ex-drinkers Men Women
	Self-reported poor health	
Palmore 1973	[illegible] volunteers, aged [illegible] years	Total
Wilhelmsen and Eriksson 1981	[illegible] adults aged 27–64 years, National Search of Prevalent Health Disorders and Consequences	Men Women
Selick et al. 1986	[illegible] women aged [illegible] years	Men Women
Pearson et al. 1987	884 HMO[b] enrollees, mean age 50 years	Total
Gilmore et al. 1989	[illegible] [illegible] and [illegible] years	Total
Haapanen and Wanner 1994	1990 U.S. National Health Interview Survey, [illegible] aged [illegible] years	Total
Poikolainen et al. 1996	[illegible] men and women, Finland, aged 25–64 years	Total

[a]OR = Odds ratio.
[b]HMO = Health maintenance organization.

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
3.31	2.56	29.3	None
3.58	2.58	[illegible]	
3.14	2.57	[illegible]	
2.62	2.42	8.3	
[illegible]	[illegible]	27.0	OR*
25.2	21.5	17.2	None
[illegible]	[illegible]	7.6	Controlled for menstrual levels, local alcohol and treatment centers, social drinkers were matched after participation. Ambulatory controllers were excluded.
[illegible]	[illegible]	4.1	
[illegible]	[illegible]	28.0	
28.6	22.4	14.0	Percentage who rate their health as worse than that of peers their age
[illegible]	[illegible]	16.1	Percentage with a physical health status score of 1.5 or more
[illegible]	[illegible]	9.4	Number of health conditions
[illegible]	[illegible]	3.4	
74.6	79.5	85.2	Percentage reporting fair/poor health
82.1	91.1	90.1	Percentage reporting poor/poor health
[illegible]	[illegible]	[illegible]	
1.62	1.0	62.0	OR
49.4	43.1	15.9	Percentage reporting subpar [illegible] health

Table 6.12 Continued

Study	Population	Group
	Self-reported poor health	
Bobak et al. 1998	Sample of 1,599 Russians, aged >18 years	Total
Dongxiao et al. 1999	1992–1993 Shanghai Population Health Survey; [illegible]	Total
	Self-perceived good/excellent health (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa; East Boston; New Haven; Piedmont Women: Iowa; East Boston; New Haven; Piedmont
York and Hurd 1993	125 alcohol drinkers, alcoholic and social drinkers, aged 20–59 years	Alcoholics Men Women Social drinkers Men Women
	Self-perceived good physical function (% reporting)	
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa; East Boston; New Haven; Piedmont Women: Iowa; East Boston; New Haven; Piedmont
	Physical health status	
Heller and Swanson 1992	Random sample of Australians only; Canberra residents, aged >20 years	Men Women
Reed 1983	582 HMO enrollees	Total

Results			
Smokers	Nonsmokers	Percentage difference	Comments
1.29	1.0	29.0	OR was adjusted for age, gender, education, alcohol, and marital status
[illegible]	[illegible]	[illegible]	OR [illegible]
64.4	74.6	[illegible]	None
58.0	69.1	[illegible]	
54.8	68.8	-20.9	
42.8	60.1	-28.8	
58.3	72.6	-19.7	
59.1	54.3	8.9	
[illegible]	60.8	-9.2	
[illegible]	51.9	-1.7	
[illegible]	[illegible]	[illegible]	Health [illegible]
[illegible]	[illegible]	10.5	
[illegible]	[illegible]	-4.1	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	-18.2	None
[illegible]	[illegible]	-17.0	
64.0	71.0	-9.7	
56.3	71.5	-21.2	
42.5	61.5	-30.9	
49.4	45.8	7.9	
49.0	57.1	-14.4	
45.1	50.9	-2.9	
[illegible]	[illegible]	[illegible]	
0.47	0.47	[illegible]	Higher score = [illegible] health
0.48	[illegible]	[illegible]	[illegible]
0.50	0.49	2.0	Higher scores [illegible] physical health status, measured by ridits (mean rank sums); age and gender adjusted

Table 6.12 Continued

Study	Population	Group
	Physical health status	
Pearson et al. 1987	864 HMO enrollees, mean age 52 years	Total
Winefield and Rich 1983	2,903 Australians	Total
	General health status (health status questionnaire Short Form-36 [SF-36])	
Wakefield et al. 1995	[illegible]	Ages [illegible] years Ages [illegible]
Shipley et al. 1993	818 HMO members with asthma	Total
	Life dissatisfaction	
Kaprio and Koskenvuo 1988	7,094 Finns, twin cohort, men aged 20–54 years, women aged 20–39 years	Men: 20–34 years; 35–54 years Women: 20–39 years
	General life satisfaction	
[illegible] 1983	504 employees, mean age 24 years	Men Women
	Overall well-being	
Dennerstein et al. 1994	Random sample of 1,503 women, Melbourne, Australia, aged 45–55 years	Total
	Overall quality of life	
Shipley et al. 1992	1,471 HMO members with asthma	Total
	Tiredness (arithmetic reversal [illegible] reporting)	
Chetwynd and Rayner 1986	Survey of 978 women who [illegible] Christchurch, New Zealand, aged 18–65 years	Total
	Getting [illegible] (% reporting)	
[illegible] et al. 1990	[illegible] and Hopkins Revised [illegible]	Total

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Results			
Smokers	Nonsmokers	Percentage difference	Comments
[illegible]	[illegible]	[illegible]	Percent reporting low physical health
[illegible]	[illegible]	[illegible]	Higher scores reflect better physical health (100 = best, 0 = worst)
71.0 69.1	77.4 74.6	-8.3 -7.4	Smokers = ever smokers
[illegible]	[illegible]	[illegible]	Higher scores reflect better mental health (100 = best, 0 = worst)
8.8 9.1 8.7	8.4 8.3 8.2	4.8 9.6 6.1	Based on a psychological scale; details were not specified
[illegible]	[illegible]	[illegible]	Age-standardized percentage with at least two chronic general medical conditions
1.43	1.57	-8.9	Higher scores reflect a greater sense of well-being
[illegible]	[illegible]	[illegible]	[illegible]
36	21	[illegible]	Scores
32	20	62.5	Age-standardized

Table 6.12 Continued

Study	Population	Group
Mental health (health status questionnaire Short Form 36 [SF-36])		
Wakefield et al. 1995	3,010 Australians, aged >15 years	Aged [illegible] years Aged [illegible] years
Sippel et al. 1995	619 HMO members in California	Total
Mental well-being		
Wooden and Bush 1992	[illegible] Australians	Total
Psychosomatic symptoms		
[illegible] Jorgensen 1989	648 persons in a [illegible] psychiatric patients, student nurses and university undergraduates	Psychiatric patients Student nurses Undergraduates Men Women
Psychological symptoms		
Macnee 1991	240 men and women, mean age 33 years	Total
Depressed mood (PSI)		
[illegible]	[illegible] Health Interview Survey, [illegible]	Men Women
Health behavior efficacy expectations, health status		
Czernbewski et al. 1993	2,523 Medicare beneficiaries	Total Total

Results			
Smokers	Nonsmokers	Percentage difference	Comments
73.6 78.0	75.2 80.6	-2.1 -2.5	Smokers = ever smokers
[illegible]	[illegible]	[illegible]	Higher scores reflect better physical health (100 = best, 0 = worst)
2.223	2.300	-3.3	Higher scores reflect better mental health (4-point scale: 4 = best)
[illegible]	[illegible]	[illegible]	Mental health indicators: Psychoneurotic Symptom Scale; scores higher or more symptomatic
6.8	7.9	11.4	Symptom checklist: range from 0–40; higher scores equal more symptoms based on 10-item measure
[illegible]	[illegible]	[illegible]	Mean
9.30 7.70	9.78 9.69	-5.1 -21.0	Scales of 0 to 10 (0 = low and 10 = high) efficacy expectations of health behaviors (exercise, dietary fat, weight control, smoking, and alcohol consumption) and resulting health status expectations

Table 6.13 Studies evaluating the dose-response relationship between the number of cigarettes smoked per day and health status

Study	Population	Group
Mean number of illnesses in the past 30 days		
Marsden et al. 1988	17,328 active U.S. military personnel	Total
Self-reported poor health status (number of health complaints)		
[illegible]	[illegible]	[illegible] Women
Subjective health complaints		
Jourdy et al. 1989	[illegible]	[illegible]
Jourdy et al. 1993	[illegible]	[illegible]
Balas [illegible]	[illegible]	[illegible]
Jourdy et al. 1992	[illegible]	[illegible]
Mundt-Babbs et al. 1999	[illegible]	[illegible]
Physical health status		
Bellis and Breslow 1982	Random sample of Alameda County, California residents, aged ≥20 years	Current smokers Men Women Former smokers Men Women
Physical health score		
Wiley and Camacho 1988	3,882 Alameda County residents, aged 20–70 years	Men Women

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Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	Comments
0	0.4	12.3	36.4	None
0	[illegible]	[illegible]	[illegible]	None
0	[illegible]	[illegible]	[illegible]	None
0	[illegible]	[illegible]	[illegible]	None
1	[illegible]	[illegible]	[illegible]	Adjusted for [illegible]
0	[illegible]	[illegible]	[illegible]	[illegible]
0	[illegible]	[illegible]	[illegible]	[illegible]
0	-75.9	-265.5	-286.2	High scores = better physical health
0	50.0	-500.0	375.0	

Table 8.13 Continued

Study	Population	Group
	Self-reported health status	
Segovia et al. 1989	Sample of 3,300 residents of St. John's, Canada, aged >20 years	Total
Polkinghorn et al. 1988; Polkinghorn et al. Waterhouse 1987	[illegible] aged 25–64 years	Total
	Impaired psychological status	
Lindenthal et al. 1972	938 New Haven adults (aged >18 years), sample	Total
	Psychological well-being	
Winefield and Tiggemann 1989	[illegible]	Total

*NR = Data were not reported.

Nonsmokers (referent)	Percentage difference: Smokers, by category of dose (1 = low) 1	2	3	Comments
0	-16.3	19.1	-31.9	Percentage reporting good health, additional smoking categories, by increasing dose [illegible]
0	[illegible]	[illegible]	NR*	Percentage reporting suboptimal health
0	35.8	-23.8	50.3	Based on a percentage with very impaired status; smoking frequency categories
0	[illegible]	[illegible]	NR	None

Table 8.14 Studies comparing the health status of former smokers and nonsmokers

Study	Population	Group
	Perceived poor health	
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
	Self-reported poor health (number of health complaints)	
Seidell et al. 1986	[illegible] aged 15–60 years	Men; Women
	Subjective health complaints	
Lilienfeld 1958	[illegible]	Total
Joung et al. 1995	[illegible] aged 25–74 years	Total
	Poor health	
Balarajan et al. 1985	United Kingdom [illegible] years	Quit >1 year; Quit ≤1 year
	Confidence	
Joung et al. 1995	[illegible]	Total
	Physical symptoms	
Macrae 1991	[illegible]	Total
	Concern about physical health (% reporting)	
	[illegible]	Total
	Getting very tired easily (% reporting)	
Rimer et al. 1990	3,147 American Association of Retired Persons members, aged 50–102 years	Total

*OR = Odds ratio.

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Results			
Former smokers	Nonsmokers	Percentage difference	Comments
1.35	1.0	35.0	OR*
[illegible]	[illegible]	[illegible]	[illegible]
18.9	9.1	9.8	[illegible]
[illegible]	[illegible]	[illegible]	OR
[illegible]	[illegible]	[illegible]	OR
1.47	1.0	47.0	OR
38.[illegible]	[illegible]	[illegible]	[illegible]
41	30	33.3	None
25	20	25.0	Age-adjusted

Table 8.14 Continued

Study	Population	Group
Self-reported poor health		
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,033), aged >17 years	Time since cessation 0–2 months 3 months–1 year 2–4 years 5–10 years >11 years Current
[illegible]	[illegible]	Total
Self-reported health status		
Orleans [illegible]	[illegible]	Total
[illegible]	[illegible]	Total
General health status (health status questionnaire Short Form 36 [SF-36])		
Sippel et al. 1999	613 HMO† members with asthma	Total
Self-perceived good/excellent health (% reporting)		
Culshier et al. 1990	Population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont

†HMO = [illegible]

Results			
Former* smokers	Nonsmokers	Percentage difference	Comments
			OR
3.03	1.0	203.0	
2.83	1.0	183.0	
2.01	1.0	101.0	
1.35	1.0	35.0	
1.42	1.0	42.0	
1.00	1.0	0.0	
1.[illegible]	1.0	[illegible]	[illegible]
22.5	11.3	99.1	Percentage fair/poor
[illegible]	[illegible]	[illegible]	[illegible]
61	66	-7.6	Higher score = better health status (100 = best, 0 = worst)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Table 8.14 Continued

Study	Population	Group
Good physical function (% reporting)		
Culshier et al. 1990	6 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont
Physical health status		
Fielder and Eberhart 1972	Random sample of Alameda County, [illegible]	Men Women
Reed 1983	812 HMO enrollees	Total
Wrenden and Bosh 1995	2,213 Australians	Total
Overall quality of life		
Sippel et al. 1999	613 HMO members with asthma	Total
Mental health (health status questionnaire Short Form 36 [SF-36])		
Nystrom et al. 1999	619 [illegible]	Total
Psychological symptoms		
Macnee 1991	241 [illegible]	Total
Impaired psychological status		
[illegible]	9,872 [illegible]	Total
Mental health: prevalence of psychiatric morbidity		
Stansfeld et al. 1993	9,962 men and women, Whitehall Study, aged 35–55 years	Men Women

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Results			
Former smokers	Nonsmokers	Percentage difference	Comments
60.4	70.5	-14.3	None
58.6	64.2	-8.7	
65.7	71.0	-7.5	
64.2	71.5	-10.2	
49.0	[illegible]	-20.3	
44.9	[illegible]	-2.0	
47.9	[illegible]	-16.1	
49.8	[illegible]	-2.2	
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
2.4	1.8	33.3	Higher scores reflect a poorer quality of life (10-point scale, 10 = worst)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
11.8	7.9	49.4	None
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
28.1	23.7	18.6	Smoking was also associated with a risk of
30.6	30.0	0.3	physical symptoms in both genders

Table 6.14 Continued

Study	Population	Group
	Feeling discouraged/blue (depression)	
Lilienfeld 1959	903 residents, Buffalo, New York	Total
	Psychological well-being	
Weissman and Paykel 1989	6,913 U.S. adult female patients	Total
	Mental well-being	
Wannamethee and Shaper 1995	5,018 Australians	Total
	Life dissatisfaction	
Rahkonen et al. 1988	7,064 Finnish urban employed men aged 30–64 years; 96 men aged 30–39 years	Men: 30–39 years; 40–64 years
		Women: 30–39 years; 40–64 years
	General life satisfaction	
Blair et al. 1980	504 employees, mean age 34 years	Men Women

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
32.9	24.8	32.7	Percentage sometimes/very often
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	Higher scores reflect better well-being (1–30 point scale, 1 = best)
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	Based on a psychological scale
[illegible]	[illegible]	[illegible]	[illegible]
27.5	32.8	-16.4	None
20.5	35.4	-42.1	

Loss of Bone Mass and the Risk of Fractures

In the United States, of the estimated 650,000 fractures per year in persons 65 years of age and older, nearly 300,000 are hip fractures (Apple and Hayes 1994; Centers for Disease Control and Prevention [CDC] 1996; Ray et al. 1997). Approximately 33 percent of women and 17 percent of men experience a hip fracture if they live to be 90 years old (Mazess 1982; Melton and Riggs 1987). Mortality in persons with a hip fracture is 12 to 20 percent higher than in persons without a hip fracture of similar age, race, and gender (Miller 1976; Jensen and Tondevold 1979; Weiss et al. 1983; Jensen 1984; Kenzora et al. 1984; Kreutzfeldt et al. 1984). The estimated annual costs for medical and nursing services related to hip fractures range from $7 billion to $10 billion (Ray et al. 1997). From July 1991 through June 1992, costs to Medicare for 10 types of fractures were estimated at $4.2 billion (Baron et al. 1996). Moreover, continued growth of the elderly population can be expected to dramatically increase the number of hip fractures, because hip fracture incidence rates increase exponentially with age (Melton and Riggs 1987; Melton et al. 1987). If these demographic and incidence trends continue, the number of hip fractures may well double or triple by the middle of the century (Kelsey and Hoffman 1987). With their frequency, adverse quality of life impacts, and economic costs, hip fractures are an urgent and major public health problem.

Bone mineral density (BMD) is one of the strongest indicators of the risk for a fracture. Several cohort studies have confirmed that even a single low BMD measurement is associated with the risk of a hip fracture (Gardsell et al. 1989; Hui et al. 1989; Cummings et al. 1993). For each standard deviation decrease in BMD, the estimated relative risk (RR) of fractures ranged from 1.5 to 2.5, depending on the site that was measured (Marshall et al. 1996). Therefore, discussions of the possible adverse effects from smoking on bone health should consider both BMD and fractures as outcome measures. An estimated 60 to 80 percent of the bone density variation is explained by genetic factors (Eisman 1999), leaving 20 to 40 percent of the variation attributable to nongenetic factors. Smoking is an important modifiable risk factor in both women and men.

Conclusions of Previous Surgeon General's Reports

Harmful effects of smoking on the skeleton have been recognized for several decades but the data were not sufficient to conclude that smoking adversely affects bone mass (USDHHS 1990); however, the most recent Surgeon General's report on women and smoking (USDHHS 2001) identified smoking as adversely affecting bone health and increasing the risks for fractures. The report concluded that smoking adversely affects bone density and increases the risks for hip fractures in postmenopausal women. Specifically, the conclusions were that (1) postmenopausal women who currently smoke have lower bone density than women who do not smoke; (2) women who currently smoke have an increased risk for hip fracture compared with women who do not smoke; and (3) the relationship among women between smoking and the risk for bone fracture at sites other than the hip is not clear (USDHHS 2001). However, because male osteoporosis also has been recognized as a considerable disease burden, the role of smoking in male bone health also deserves consideration.

Biologic Basis

Smoking has the potential for direct and indirect effects on skeletal health and the risk of fractures. Direct toxic effects of smoking on bone cells may be related to the physiologic effects of nicotine (Fang et al. 1991; Riebel et al. 1995) or possibly cadmium in tobacco smoke (Bhattacharyya et al. 1988). Indirect effects of smoking on bone cells may result from decreased intestinal calcium absorption (Krall and Dawson-Hughes 1999), reduced intake and lower levels of vitamin D (Brot et al. 1999), or alterations in the metabolism of adrenal cortical and gonadal hormones (Michnovicz et al. 1986; Khaw et al. 1988; Baron et al. 1995). These direct and indirect effects may account for the generally observed decrease in markers of bone formation such as osteocalcin in smokers compared with nonsmokers (Brot et al. 1999; Bjarnason and

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Christiansen 2000). Smoking might also indirectly influence bone density through reduction in body weight, since body weight tends to be lower for smokers than for nonsmokers. This weight difference may itself lead to lower bone density and an increased risk for a fracture (Kiel et al. 1987; Cummings et al. 1985). Smokers also tend to have an earlier menopause than nonsmokers, thus extending the postmenopausal period of accelerated bone mineral loss (USDHHS 2001). Finally, smokers tend to be less physically active than nonsmokers and activity level is associated with bone density and hence risk for a fracture (Gregg et al. 1998).

In several analyses involving women, the lower weight of smokers compared with nonsmokers explains part of the increased risk for low BMD associated with smoking (Bauer et al. 1993). However, there are differences in BMD and in fracture rates between smokers and nonsmokers even after adjusting for weight differences, suggesting that the weight difference alone does not explain the effects of smoking (Kiel et al. 1992, 1998; Bjarnason and Christiansen 2000). The lower weight in smokers may increase the risk of fractures, such as hip fractures, through several mechanisms, including [illegible] soft tissue mass overlaying the trochanter resulting in lower energy absorption from a fall on the hip, reduced weight loads on the skeleton, or reduced conversion of adrenal steroids into sex steroids in adipose tissue. The antiestrogenic effect of smoking also may contribute to osteoporosis in women (Jensen et al. 1985; Jensen and Christiansen 1988), and may reduce the benefits of hormonal replacement therapy (Komulainen et al. 2000). In a Finnish trial of osteoporosis prevention, smoking was associated with a nonresponse to hormonal therapy, as assessed by changes in BMD (Komulainen et al. 2000). Less consistent evidence for a blunted response to estrogen by smoking was reported from a Danish trial (Bjarnason and Christiansen 2000). Interestingly, although estrogen appears to be a critical hormone for male skeletal health (Slemenda et al. 1997; Khosla et al. 1998), smoking does not appear to modify the association between estradiol levels and bone density in men (Amin et al. 1999). Finally, smoking may increase the risk of fractures through reductions in physical performance capacity, thereby increasing the risk for falls (Nelson et al. 1994).

Bone Density in Young Men and Women

Epidemiologic Evidence

Increasingly refined measures of BMD have become available so that current studies use direct BMD measurements. Before such direct measurements were possible BMD was assessed using radiographs, with measurements typically focused on the widths of the cortical bones in sites such as the metacarpals. Direct quantitative assessments of the amount of mineral in various skeletal sites have now become possible with the advent of single and dual photon absorptiometry, followed by refinements such as single and dual x-ray absorptiometry, quantitative computed tomography, and quantitative ultrasonography. These techniques have all been used to generate the data summarized here.

In adults at any particular age bone mass is dependent on the peak mass achieved up to that age, and subsequent losses from the peak are attributable to aging and other factors. The pace of skeletal growth is rapid during infancy, slower during childhood, accelerated during puberty, and by 20 to 30 years of age the peak skeletal mass is attained (Kroger et al. 1992; Lu et al. 1996). Gains in BMD continue into the third decade after bone growth has ceased (Recker et al. 1992). After menopause, bone loss rates accelerate compared with premenopausal rates, and these rates are sustained or increase even more with aging (Ensrud et al. 1995). Age-related losses also occur in men (Jones et al. 1994). In the context of these age-related patterns, the role of smoking in the attainment of peak bone mass is reviewed along with studies of bone density and menopausal status. A literature search was conducted using the National Library of Medicine's PubMed system; the key words used were "bone mineral density," "bone density," "fracture," "smoking," and "cigarettes." In addition, all references from a key meta-analysis (Law and Hackshaw 1997) were also retrieved. Studies focusing on men mainly involve older age groups. The evidence on smoking and BMD comes primarily from cross-sectional and cohort studies. The cross-sectional studies assess the cumulative consequences of smoking on BMD growth and/or decline. Cohort studies can assess changes in BMD over time. Findings of the different types of studies are presented in Tables 6.15–6.17.

Table 6.15 Cross-sectional studies on the association between smoking status and bone density in women*

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
Premenopausal			
Fehily et al. 1992	22 (20–23)	104 current smokers 75 never/former smokers	Radius
[illegible] et al. 1994	28 (23–30)	5 current smokers 47 never smokers	Femur
[illegible] et al. 1994	28 (20–35)	15 current smokers 32 never/former smokers	Femur
[illegible] et al. 1994	28 (SD = 2)	41 current smokers 41 never/former smokers	Femur
[illegible] et al. 1992	29 (20–35)	29 current smokers 32 never/former smokers	Femur
[illegible] et al. 1989	30 (20–39)	33 current smokers 103 never/former smokers	Femoral neck, spine, and radius
Sowers et al. 1993	30 (22–36)	41 current smokers 23 never/former smokers	Radius
[illegible] et al. 1992	31 (25–39)	92 current smokers 72 never smokers	Radius
	31 (20–44)	92 current smokers 115 never smokers	Radius
	31 (25–39)	92 current smokers 102 never smokers	Radius
	32 (20–34)	114 current smokers 75 never smokers	Radius
Hopper and Seeman 1994	33 (22–42)	5 current smokers [illegible] never smokers	Spine
Christiansen et al. 1984	40 (40)	186 current smokers 186 never/former smokers	Forearm

[illegible] the weight of the evidence in this table reflects the order of presentation in Figure [illegible]

*BMD = Bone mineral density.
†SD = Standard deviation.
‡CI = Confidence interval.
§BMC = Bone mineral content.

Findings
No differences in BMD† between smokers (0.71 g/cm² [SD‡ = 0.07]) and nonsmokers (0.71 [0.06])
Mean BMD in g/cm² (SD) at hip = 0.914 (0.104) for smokers compared with 0.956 (0.110) for nonsmokers, adjusted for age, weight, and exercise
Mean BMD in g/cm² = [illegible] for smokers compared with [illegible] for nonsmokers
Femoral neck BMD in g/cm² (SD) for smokers = [illegible]; nonsmokers = [illegible], p < 0.05. Lumbar spine for smokers = [illegible]; nonsmokers = [illegible], p = [illegible]
Mean BMD in [illegible] adjusted for [illegible]
Spine BMD was significantly lower [illegible] compared with nonsmokers (p < 0.05).
Radius BMD was [illegible] = 0.71 g/cm² for smokers compared with 0.74 (0.08) for nonsmokers (p < 0.05)
[illegible] between current smokers and nonsmokers = 0.41 (95% CI‡ = 0.23–0.59)
Study of twins [illegible]
[illegible] BMC§ in [illegible] = 73. The [illegible] compared with 118 g/cm² for nonsmokers, a loss of 45% [illegible]

Table 6.15 Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
Postmenopausal			
Law et al. 1997	45 (39–49)	24 current smokers 56 never smokers	Radius
	52 (50–54)	31 current smokers 83 never smokers	Radius
	57 (55–59)	32 current smokers 135 never smokers	Radius
	62 (60–64)	27 current smokers 65 never smokers	Radius
[illegible] and Christiansen 1988	50 (41–59)	37 current smokers 42 never/former smokers	Radius
[illegible] et al. 1985	[illegible]	[illegible] current smokers [illegible] never/former smokers	Radius
[illegible] et al. 1989	62 (45–79)	33 current smokers 63 never/former smokers	Rib [illegible] lumbar spine
McDermott et al. 1990 Watts 1995	50 (SD = 10)	24 current smokers 24 never smokers	Radius
Premenopausal			
Politzer et al. 1995	54 (48–59)	7 current smokers [illegible] never/former smokers	Femur
Chung et al. 1991	54 (50–60)	25 current smokers [illegible] never/former smokers	Forearm
Reid and Dawson-Hughes 1991¶	59 (40–70)	35 current smokers 292 never/former smokers	Femur
Hopper and Seeman 1994	62 (50–74)	7 current and [illegible] 7 nonsmokers	Femur

*BMD = Bone mineral density.
†SD = Standard deviation.
‡BMC = Bone mineral content.
§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

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Findings
Difference in BMD[a] between current smokers and nonsmokers = −0.17 g/cm² (95% CI: −1.88, 1.54)
[illegible]
BMC[b] [illegible]
For current smokers, adjusted annual change in bone density was −0.0054 g/cm² (SD = 0.0159) [illegible]
BMD[c] [illegible]
Mean BMD [illegible]
Study of twins discordant for tobacco use, by menopause status. BMD was lower for the twin who smoked more heavily

Table 6.15 Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
		Premenopausal	
Sowers et al. 1985	32 (25–30)	119 current smokers 278 never smokers	Radius
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Johansson et al. 1987	29 (20)	[illegible]	[illegible]
Hreshchyshyn et al. 1988	30 (26)	45 current smokers 245 never smokers	Calcaneus
	35 (26)	54 current smokers 364 never smokers	Calcaneus
	30 (26)	45 current smokers 218 never smokers	Calcaneus
Bauer et al. 1989	31 (22–36)	155 current smokers 4,062 never smokers	Radius
Slemenda et al. 1990	34 (30–39)	76 current smokers 305 never smokers	Femur
[illegible]	35 (32)	15 current smokers [illegible]	Calcaneus
Hollenbach et al. 1993	36 (30–39)	43 current smokers 240 never smokers	Femur

[a]BMD = bone mineral density.
[b]SD = Standard deviation.
[c]BMC = Bone mineral content.

Findings
Mean BMD[a] = 0.633 (SD[b] = 0.014) for smokers of 1–9,000 pack-days, and 0.637 (SD = 0.014) for >9,000 pack-days compared with 0.635 (SD = 0.005) for nonsmokers (findings were not significant); adjusted for age, [illegible] years and median muscle mass
[illegible]
Mean [illegible]
Study of 41 [illegible]
Among 73 premenopausal current smokers, BMD [illegible]
Women [illegible]
Current smokers [illegible]
Current smokers had [illegible]
Comparison between [illegible]

Table 6.16 Studies on the association between smoking status and bone density in men and women published since the 1997 meta-analysis by Law and colleagues

Study	Population/age (years)	Smoking status	Measurement/site
		Women	
Brot et al. 1997	433 perimenopausal Danish women aged 45–58 years; 87 were followed for	49% current smokers 39% never smokers 12% former smokers	A BMC[c] of the whole body was measured at enrollment and after 1 and 2 years
[illegible]	[illegible]	[illegible]	[illegible]
Grainge et al. 1998	950 postmenopausal women aged 45–65 years	21% current smokers [illegible]	BMD at the spine, hip, [illegible] whole body
Slemenda et al. 1998	2,935 perimenopausal white Dutch women aged 18–54 years	36% smokers, women or current smokers were found to be [illegible]	BMD at the spine
Chapurlat et al. 1999	600 white women aged 50–75 years	49% had a history of cumulative smoking of 8.2 pack-years [illegible] current smokers	BUA[d] at the calcaneus
Cornuz et al. 1999	903 women aged 45–58 years; 12.2+ generations [illegible] were postmenopausal	12% current smokers	BUA and SOS[e] of the calcaneus; BMD at the spine and hip
Jones and Scott 1999	765 premenopausal women [illegible]	45% current smokers	BMD at the spine, hip, and calcaneus
Varenna et al. 1999	[illegible]	21.9% never smokers [illegible] current smokers 20.1% former smokers	BMD at the spine

[a]BMC = bone mineral content.
[b]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[c]BMD = Bone mineral density.
[d]BUA = Broadband ultrasound attenuation.
[e]SOS = Speed of sound.

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Findings

Smoking (pack-years[1]) was a significant and independent predictor of total BMC ($p < 0.001$)

Table 6.16 Continued

Study	Population/age (years)	Smoking status	Measurement/site
Women			
Kim et al. 2000	238 Korean women; mean age 24.2 ± 2.5 years scanned only as a reference population 552 postmenopausal Korean women; mean age 62.5 ± 8.2 years	Data were not reported	BUA[2] of the calcaneus
Men			
Vogel et al. 1997	1,581 men of Japanese descent in Oregon, Hawaii, aged 61–68 years	29% never smokers 43% former smokers 28% current smokers	BMD[1] of the radius, femoral neck, and lumbar spine; DXA
Hayakawa and Tominaga 1999	1,078 Japanese men aged 50–64 years	[illegible] never smokers [illegible] former smokers [illegible] current smokers	DXA of the lumbar spine
Thorsteinsson et al. 2000	149 Finnish men aged 54–61 years	Mean pack-years = [illegible]; range = [illegible]	BMD of the neck, trochanter, Ward's triangle, and [illegible]

[1]BMD = Bone mineral density.
[2]BUA = Broadband ultrasound attenuation.

Findings

There was no association between a history of smoking and low quantitative ultrasound values after controlling for age and time since menopause

Table 6.17 Cohort studies on the association between smoking status and the risk of bone loss in men and women

Study	Population/age (years)	Smoking status	Measurement/site
Slemenda et al. 1989	84 perimenopausal and postmenopausal women followed for 3[illegible] years	Data were not reported	BMD[1] of the pala[illegible] distal radius, and the lumbar spine
Krall and Dawson-Hughes 1[illegible]	3[illegible] postmenopausal women aged 40–70 years; 2-year observational period	[illegible] current smokers [illegible] former smokers [illegible] never smokers [illegible]% smoked during study or part of the period	BMD of the radius, [illegible] and the spine
Sowers et al. 1992	111 white women aged World War II or the Korean War born between 1916 and 1927, all twin pairs; 16-year follow-up	[illegible]	BMD of the radius
Sowers et al. 1993	217 women aged [illegible] years; 2-year follow-up	Mean lifetime pack-years = [illegible]	BMD of the [illegible] radius
Johnell et al. 1994	637 [illegible] men aged [illegible] years; average follow-up was [illegible] years	Women had a median of 9 pack-years of smoking; men had a median of 31 pack-years of smoking	BMD of the hip and the spine
[illegible] et al. 1997	1,503 Japanese American men aged 71–82 years; average follow-up was [illegible] years	[illegible] current smokers [illegible] former smokers [illegible] never smokers	BMD of the [illegible] proximal femur and the [illegible] radius
[illegible] 1998	[illegible] Dutch men (mean age, 68.7 years), 2,452 Dutch women (mean age 67.2 years); average follow-up was 2 years	Current smokers Men (23%) Women (19%)	BMD of the hip

[1]BMD = Bone mineral density.
[2]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

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Source: https://www.industrydocuments.ucsf.edu/docs/skmj0001

Findings

Her[illegible] smokers (>20 pack-years?) had significantly (p = 0.01) lower radial (midradius = 0.76 [standard deviation (SD) = 0.08] g/cm², ultradius = 0.83 [±0.12] g/cm²) and vertebral (lumbar spine = 0.82 [±0.16] g/cm²) BMD than nonsmokers (0.81 [±0.11], 0.91 [±0.13], and 0.94 [±0.15] g/cm², respectively). There were no significant differences between light smokers (<20 cigarettes/d) and [illegible] nonsmokers in [illegible] BMD.

Adjusted mean radial annualized rate of bone change from baseline was greater among smokers than nonsmokers (−0.014 [±2.24]% versus 0.004 [±2.08]%; p = 0.02). Body size (BMI), [illegible] variables related to muscle development (type of activity, strength, isometric muscle force), alcohol consumption, and oral contraceptive use did not significantly modify the observed association between smoking and bone loss.

[illegible] (−0.196 [±0.196] [p = 0.002] for [illegible] smoking; the twin who smoked more lost more bone [p = 0.005]); men with cigarette and alcohol use above median levels had the most rapid losses.

[illegible] women (80–86 perimenopausal, 86 premenopausal) at baseline were compared with a follow-up [illegible]

There were no differences in bone loss between smokers and nonsmokers.

Compared with never smokers, current smokers had significantly greater rates of bone loss (2.4% from the subsequent year [p = 0.001] and 2.8% from other estimates [p = 0.01]). Bone loss was also related to average weekly alcohol consumption, but not to body mass or dietary calcium intake.

Smoking was associated with a significantly higher rate of bone loss in both men and women (men, p = 0.02; women, p = 0.1); the association was stronger when not adjusting for body mass index.

Table 6.17 Continued

Study	Population/age (years)	Smoking status	Measurement/site
Guthrie et al. 1998	224 women (74 premenopausal, 90 perimenopausal, and 60 postmenopausal); follow-up was 2 years	Premenopausal women 14% current smokers Early perimenopausal women 14% current smokers Late perimenopausal women 25% current smokers Postmenopausal women 16% current smokers	BMD* of the hip and the spine
Kiel and Dawson-Hughes 1989	402 elderly men and women (302 smokers; 50% nursing-home residents; [illegible] control-based study)	Smokers 42% men 58% women Nonsmokers 47% men 53% women	BMD [illegible] and the spine
Hannan et al. 2000	466 women, 276 men (mean age 74.5 years); average follow-up was 4 years	Current smokers Women (10%) Men (8%)	bMD of the hip, spine, and radius

*BMD = Bone mineral density.

Findings

Of the women who became postmenopausal during the study, 6 were current smokers and their mean annual change in spine BMD was slightly greater (−3.3%) than that of the 36 nonsmokers (−2.3%); p = 0.10.

[illegible] BMD were lower in the lumbar spine BMD in adult male supplementation eating and dietary [illegible] and were higher in smokers than in nonsmokers in the femoral neck (0.714 g/cm²) in smoker group = 0.69 [±0.1] g/cm²; p = 0.004) [illegible] and total body (1.020 [±0.1] g/cm² versus 0.952 [±0.1] g/cm²; p = 0.005). There were no significant differences in the spine (0.880 [±0.2] g/cm² in smokers versus 0.904 [±0.2] g/cm² in nonsmokers; p = 0.2).

Compared with women who had never used [illegible] current smokers had [illegible] loss in bone (−1%), in men, current smokers had greater bone loss (−1.2%) than never smokers.

Peak Bone Mass

Because BMD increases rapidly during adolescence, initiating smoking around the time of puberty might reduce peak BMD. However, the effects of smoking on the attained level of peak bone mass are uncertain because there are limited data on the skeletal effects of smoking during adolescence. Furthermore, it is possible that relatively short exposures in this age group would have little effect on bone density measurements. One prospective cohort study of children and adolescents (aged 9 to 18 years) in Finland repeatedly ascertained lifestyle factors and followed participants for 11 years, at which time they underwent bone density testing (Välimäki et al. 1994). In men, but not in women, smokers had lower BMD measurements of the hip and spine than did nonsmokers after adjusting for covariates. A cross-sectional study of 15-year-old Swedish adolescents did not find an association between smoking and total body bone mineral content (Leibarn et al. 1998). Findings were similar in a cross-sectional study of 500 children aged 4 to 20 years in the Netherlands, but only 32 were smokers (Boot et al. 1997).

Data are available from studies of premenopausal women, starting from the ages at which peak BMD is reached. A meta-analysis of cigarette smoking, BMD, and the risk for hip fractures (Law and Hackshaw 1997) identified 10 cross-sectional studies of premenopausal women (Johnell and Nilsson 1984; McCulloch et al. 1986; Mazess and Barden 1991; Daniel et al. 1992; Fehily et al. 1992; Sowers et al. 1992; Hopper and Seeman 1994; Ortego-Centeno et al. 1994; Välimäki et al. 1994; Law et al. 1997). Additional study populations included menopausal and postmenopausal women (Table 6.15). As shown in Table 6.15, the mean ages of women in the study samples ranged from 22 to 70 years. Because absolute bone density units varied among studies according to the bone site assessed and the measurement technique used, the difference between the average BMD of current smokers and nonsmokers in each of the studies was recorded as a proportion of one between-person standard deviation. In combining the studies, each bone density difference was weighted by the inverse of its variance and was age-adjusted only.

Bone densities were reported for current smokers compared with never smokers in most studies, but were reported for current compared with former and lifetime never smokers combined in a few studies. There was no evidence of a significant difference in BMD between smokers and nonsmokers in the premenopausal women (Figure 6.2). Two additional studies of premenopausal and postmenopausal women performed since the 1997 meta-analysis also show no significant differences in BMD between smokers and nonsmokers (Table 6.16) (Takada et al. 1997; Gregg et al. 1998); however, a study of premenopausal women from Australia did find a significantly lower BMD in female current smokers that was not found in the subgroup of female smokers who participated in sports (Jones and Scott 1998). Cross-sectional data from the Danish Osteoporosis Prevention Study showed lower BMD in current smokers compared with lifetime nonsmokers in perimenopausal women (Hermann et al. 2000). It is appropriate to consider these results unadjusted for other covariates in that adjusting for one of the most important risk factors for bone density—weight—actually may mask an association. Smoking-induced weight loss may represent an intervening variable in the causal chain between smoking and bone density reduction.

One study from Spain assessed smoking and BMD in healthy young males (Ortego-Centeno et al. 1997). In this study, male volunteers aged 20 through 45 years were measured for BMD in the lumbar spine and proximal femur. blood biochemical markers were also assessed. BMD was significantly lower for smokers of 20 or more cigarettes per day compared with nonsmokers. In multiple regression analyses considering all smokers, smoking was not significantly associated with measures of BMD. Interpretations of these findings are limited by the cross-sectional data and the small sample size.

Smoking Cessation and Bone Mineral Density Loss

Two prospective cohort studies assessed smoking cessation and BMD in men and women (Hollenbach et al. 1993; Kiel et al. 1996). In a study in Rancho Bernardo, California, Hollenbach and colleagues (1993) found that smoking cessation later in life was beneficial for men and women in halting BMD loss at hip sites (intertrochanter, total hip, femoral neck, and trochanter) where BMD is reduced in smokers. In men, smoking cessation was followed by a reduction in the rate of loss of the spinal BMD, and women experienced a significant decrease in the rate of BMD loss at the midradius after quitting. In the Framingham study, current or former smoking (past 10 years) was not associated with a lower BMD loss at any skeletal site among women who had not taken estrogen but it was in women who had (Kiel et al. 1996). Former male smokers who had quit for less than 10 years had a lower BMD than men who had quit for 10 or more years, independent of weight, alcohol consumption, or caffeine use.

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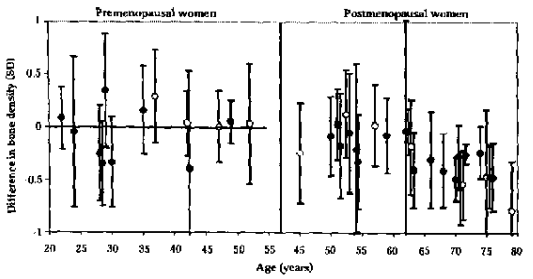
Source: https://www.industrydocuments.ucsf.edu/docs/skmj0001

Figure 6.2 Differences (95% confidence intervals), as a proportion of 1 standard deviation (SD), in bone mineral density between female smokers and nonsmokers according to age and menopausal status



Note: Fitted regression curves are shown. The 11 open circles refer to two studies (Rundgren and Mellström 1984; Law et al. 1996) in Table 6.15; solid circles refer to the other studies in the order listed in Table 6.15 (Felsky et al. 1982 through Johnell and Nilsson 1993 for premenopausal women, and Law et al. 1997 through Hollenbach et al. 1993 for postmenopausal women).
Source: Law and Hackshaw 1997, p. 843. Reprinted with permission.

Evidence Synthesis

Smoking, even at a young age, might increase risk for osteoporosis later in life if it reduces the peak bone mass attained, thereby compromising the peak from which decline begins. Only a few studies address smoking during adolescence, and the findings in women during the premenopausal years are conflicting, are not based on large studies, and do not provide strong evidence for an effect of smoking on BMD before menopause. For males, data are scant for this age range. Although an effect of smoking on BMD is plausible, the available evidence from observational studies is limited and inconsistent.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

Implications

The failure to demonstrate a causal relationship between smoking and bone density in young women does not detract from the basis for concern about smoking and osteoporosis in women. For women, smoking patterns established in younger years are likely to persist past menopause, and there is substantial evidence linking smoking to low bone density during menopause (see below). Future research should quantify the combined and cumulative effects of premenopausal and postmenopausal smoking on bone density. More research is needed in young men regarding the relationship between smoking and bone density.

Bone Density in Middle and Later Years of Life

Epidemiologic Evidence

In contrast to the findings for younger persons, findings of bone density studies performed in populations well beyond the years of peak bone mass demonstrate substantial differences between smokers and nonsmokers. As illustrated in Figure 6.2, based on the meta-analysis by Law and Hackshaw (1997), bone density was lower in smokers than in nonsmokers for postmenopausal women, and the difference increased linearly with age. For every 10-year increase in age, the bone density of smokers fell below that of nonsmokers by approximately 2 percent of the average bone density at the time of menopause, regardless of the skeletal site that was measured.

Since the publication of this meta-analysis, there have been additional studies of smoking and bone density in postmenopausal women and in men. Of four studies that did not demonstrate an association between smoking and bone density (Cheng et al. 1998; Varenna et al. 1998; Hmaidouni et al. 2000; Kiu et al. 2000), two had used quantitative ultrasound to measure bone status. Seven other studies did demonstrate statistically significant associations between smoking and BMD (Table 6.16) (Brot et al. 1997; Takada et al. 1997; Vogel et al. 1997; Grainge et al. 1998; Smeets-Goevaers et al. 1998; Hagiwara and Tsumura 1999; Hermann et al. 2000).

Data from cohort studies of older men and women also implicate smoking as a significant risk factor for bone loss (Table 6.17). Of the six studies that reported smoking data (three involving women and men, two involving women only, and one involving men only) (Sowers et al. 1992; Jones et al. 1994; Vogel et al. 1997; Burger et al. 1998; Guthrie et al. 1998; Hannan et al. 2000), three documented significantly more bone loss in female smokers than in female and male nonsmokers (Sowers et al. 1992; Burger et al. 1998; Guthrie et al. 1998), and three reported higher rates of loss among male smokers than among male nonsmokers (Vogel et al. 1997; Burger et al. 1998; Hannan et al. 2000). Interpretations of several of the studies are constrained by relatively small sample sizes and limited durations of follow-up.

Evidence Synthesis

Extensive and consistent data are available on BMD and smoking for perimenopausal and postmenopausal women and for older men. Data from cohort studies, which track changes in BMD over time, as well as from cross-sectional studies provide generally consistent evidence of increased rates of loss in postmenopausal women who smoke compared with nonsmokers. Smoking cessation appears to benefit BMD since limited data indicate higher rates of BMD loss for heavier smokers. Data are more limited for men. The 2001 Surgeon General's report (USDHHS 2001) found the evidence to be consistent for women and concluded that "Postmenopausal women who currently smoke have lower bone density than do women who do not smoke" (p. 321). There are a number of mechanisms that may underlie this finding.

Conclusions

1. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

2. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

Implications

Smoking has an adverse effect on bone density in middle and later years of life: for every 10-year increase in age, the bone density of female smokers falls below that of nonsmokers by about a 0.14 standard deviation, or 2 percent of the average bone density at the time of menopause in women. Because a 1.0 standard deviation decrease in bone density doubles the risk of fracture, and because fracture incidence increases with age (Melton and Riggs 1987; Melton et al. 1987), the proportion of all fractures attributable to smoking would be expected to increase for smokers who continue smoking into older ages. Attempts to decrease smoking as early in life as possible are likely to reduce fractures that would be caused by smoking in old age.

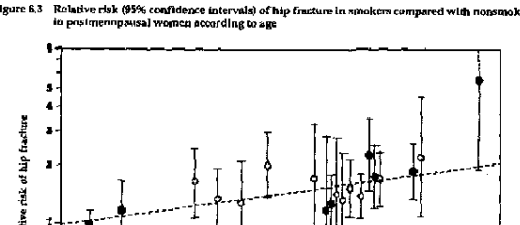
Because bone loss is relatively small over short periods of time, studies with longer durations of follow-up and minimal avoidable losses of participants at follow-up could add important information to the understanding of how smoking contributes to bone loss. Additional information is likely to come from studies of biochemical markers of bone turnover, which might further the understanding as to mechanisms whereby smoking accelerates bone loss.

Fractures

Epidemiologic Evidence

Hip fractures, the most frequently studied fractures in relation to smoking, account for a significant proportion of the morbidity and mortality attributed to osteoporosis. The meta-analysis by Law and colleagues (1997) reviewed 19 cohort and case-control studies of the risk of hip fractures in postmenopausal women according to whether they had COPDs. The studies differed with regard to the ages of the participants, duration of follow-up, and whether former smokers were included in the smoking or nonsmoking groups. Table 6.18 shows the characteristics of each of the 19 studies, demonstrating the range of ages at the time of the fracture. For the cohort studies, the duration of follow-up ranged from three years (Forsén et al. 1994) to 26 years (Kiel et al. 1992). Figure 6.3 shows the risk of hip fractures in smokers relative to nonsmokers according to age; the risks for smokers increased with increasing age. Major conclusions of the meta-analysis include (1) smoking has no material effect on bone density in premenopausal women; (2) postmenopausal bone loss is greater in smokers—an

Figure 6.3 Relative risk (95% confidence intervals) of hip fracture in smokers compared with nonsmokers in postmenopausal women according to age



Note: Each cohort study (8 solid circles) and case-control study (11 open circles) is in the same order as in Table 6.18. Fitted regression (dashed) line is shown.
Source: Law and Hackshaw 1997, p. 844. Reprinted with permission.

additional 0.2 percent of bone mass each year; (3) in comparisons of women who are current smokers with women who are nonsmokers, the risk of hip fracture is estimated to be 17 percent greater at 60 years of age, 41 percent greater at 70 years, 71 percent greater at 80 years, and 108 percent greater at 90 years; and (4) the estimated cumulative risk of hip fracture to 85 years of age in women is 19 percent in smokers and 12 percent in nonsmokers; to 90 years it is 37 percent and 22 percent, respectively. The data for men were much more limited but suggested similar consequences.

Since the publication of the meta-analysis by Law and colleagues (1997), some (Forsén et al. 1998; Burger et al. 1999; Kunis et al. 1999; Melhus et al. 1999; Baron et al. 2001) but not all subsequent studies of hip fracture (Fujiwara et al. 1997; Clark et al. 1998; Mussolino et al. 1998) have continued to show an association between smoking and an increased risk of hip fracture (Table 6.19). These studies have used various designs and have been carried out in diverse populations.

Data on the association between smoking and fractures at other sites are more limited (Table 6.20). Studies from the 1960s and early 1990s that examined fractures other than those of the hip rarely found an association with smoking, although more recent studies have demonstrated positive associations between smoking and vertebral fractures (Seane et al. 1999; Lau et al. 2000), ankle fractures (Honkanen et al. 1998), and the general categories of nonhip fractures (Jacqmin-Gadda et al. 1998) and of all fractures (Huopio et al. 2000).

Smoking Cessation and Hip Fractures

The association between smoking cessation and the risk of hip fractures was examined in several studies, including three prospective cohort studies with follow-up periods of 5 to 12 years (Forsén et al. 1998; Cornuz et al. 1999; Haldrup et al. 2000) and two case-control studies (La Vecchia et al. 1991; Cumming and Klineberg 1994). In men, successful smoking cessation of at least five years decreased the risk of hip fracture compared with continuing smokers (Haldrup et al. 2000), although other investigations found that this risk remained elevated for men and women smokers compared with lifetime nonsmokers (Cumming and Klineberg 1994; Forsén et al. 1998). Two studies also found no decrease in the risk for hip fractures in women after five years of smoking cessation (La Vecchia et al. 1991; Cornuz et al. 1999), and another found that no benefit from quitting for women, including premenopausal women, was observed until 10 years after cessation (adjusted RR = 0.7 [95 percent confidence interval (CI), 0.5–0.9] compared with current smokers) (Cornuz et al. 1999).

Evidence Synthesis

The evidence on smoking and fracture has been reviewed extensively in previous reports of the Surgeon General. The 1990 report considered evidence from eight case-control studies, noting that most showed an association with risk for fracture of the hip or vertebra. Five cohort studies, however, did not show a clear increase in risk and the report found the evidence to be inconclusive. Far more extensive data were available for the 2001 report, including substantially more studies of hip fracture in women. The case-control studies reviewed all indicated excess risk for hip fracture in smokers, with the RR ranging from 1.1 to 2.0. Six reports of cohort studies published subsequent to the 1990 report were also cited, all showing an increased risk for hip fracture in current smokers. The 2001 report (USDHHS 2001) concluded that "women who currently smoke have an increased risk for hip fracture compared with women who do not smoke" (p. 321).

This report extends the review of the 2001 report with additional studies and covers the evidence on men as well. The evidence consistently indicates an increased risk for women and men who smoke. Findings of some studies show a dose-response relationship between risk for hip fracture and the amount smoked. The RR tends to rise with age as would be expected, and the effect of smoking reflects sustained, additional bone loss beyond that associated with aging. The documented effects of smoking on BMD is consistent with the observational evidence on hip fracture.

For fracture sites other than the hip, the evidence has been less consistent. The 2001 Surgeon General's report found the evidence to be unclear. This report evaluated a number of studies for other sites, also finding the evidence to be mixed and limited in scope for any particular site.

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Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.
2. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Implications

The RR of hip fractures in smokers increases with age, and hip fracture incidence increases with age. Implying that the proportion of hip fractures attributable to smoking increases with age. Smoking is one of the major causes of fracture in older persons that can be prevented. Public health interventions aimed at helping smokers quit are likely to substantially reduce the number of hip fractures. Although hip fractures carry the greatest costs and risks of mortality and morbidity, other fractures also contribute to these outcomes. Further research is necessary to quantify the risks of these other fractures in smokers.

Table 6.18 Studies on the association between smoking and the risk of hip fractures in men and women used in the 1997 meta-analysis by Law and Hackshaw[a]

Study	Age at entry (years)	Mean age at fracture (years)	Number of persons (% smokers)	
			With fracture	Without fracture
Cohort studies				
Hennemway et al. 1988	34–59	53	682	68,056 (28)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hulbert et al. 1988	50–79	70	113	923
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings et al. 1995	≥65	79	170	[illegible]
Forsen et al. 1994	≥50	78	321 (36)	1418 (26)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Case-control studies				
Wickelgren et al. 1988	65+	84	44	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Williams et al. 1982	50–74	68	1001 (61)	967 (50)

[illegible] specific definitions used in this table [illegible]

[a]RR = Relative risk.
[b]CI = Confidence Interval.
[c]SD = Standard deviation.
[d]OR = Odds ratio.
[e]ERT = Estrogen replacement therapy.

Findings
Compared with nonsmokers, RR[a] = 0.98 [illegible] (95% CI, 0.84–1.14) for former smokers, 0.95 (95% CI, 0.71–1.20) for current smokers of 1–14 cigarettes, [illegible] (95% CI, 0.79–1.20) for current smokers of 15–24 cigarettes, and 0.90 [illegible] for current smokers of ≥25 cigarettes
[illegible]
[illegible]
[illegible]

Findings

No OR was given for smoking

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Compared with never smokers, OR for current smokers = 1.6 [illegible] **(95% CI, 0.8–2.5); for current smokers = 2.2** [illegible] **(95% CI, 1.1–4.6); adjusted for age, gender, and proxy status (when relevant)**

Table 6.19 Studies on the association between smoking and the risk of hip fractures in men and women reported since the 1997 meta-analysis by Law and Hackshaw

Study	Design	Population
Fujiwara et al. 1997	Cohort	1,586 Japanese men, 2,987 Japanese women; mean age 58.5 ± 12.2 years; during and up to the 14-year follow-up, 5 [illegible] residents of hip fracture [illegible] attributable to tr[illegible]
Grisso et al. 1997	Case-control	906 [illegible] Urban Philadelphia [illegible] [illegible]
Clark et al. 1998	Case-control	60 Chinese men and [illegible] Mexican-American women with hip fractures, age [illegible] 4 [illegible] 70.2 [illegible] 1,245 Caucasian, [illegible] middle-income controls [illegible] [illegible] with a hip fracture; mean age was 68.6 [illegible] for cases
[illegible]	Cohort	14,435 [illegible] 1,264 [illegible] women [illegible] aged 50–79 years; [illegible] 421 [illegible]
Musso et al. 1998	Cohort	[illegible] [illegible] [illegible] [illegible] [illegible] were [illegible]
Turner et al. 1998	Case-control	[illegible] 58 cases from [illegible] [illegible] [illegible] [illegible] Smokers [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
Burger et al. 1999	Cohort	[illegible] [illegible] aged [illegible] [illegible] during a [illegible] follow-up, 472 [illegible] [illegible] [illegible] [illegible]
Lorenzo et al. 1999	Cohort	[illegible] [illegible] aged [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
Kreiger et al. 1999	Cohort	[illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] were [illegible]
Kanis et al. 1999	Case-control	750 [illegible] European men with hip fractures, age ≥ 50 years (mean age 75.8 ± 11.2); age- [illegible] [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Findings

OR for hip fractures among current smokers [illegible]

OR for hip fractures among current smokers with a low intake of vitamin E was [illegible] of vitamin C, 3.0 (95% CI, 1.6–5.6); OR decreased to 1.1 (95% CI, 0.5–2.4) and 1.4 (95% CI, 0.7–3.0) with high intakes of vitamins E and C, respectively. In current smokers with a low intake of vitamins E and C, OR increased to 4.8 (95% CI, 2.2–11.0).

RR = 1.06 (95% CI = 1.02–1.09) for female and 1.02 (95% CI, 1.00–1.04) for male current smokers and ex-smokers within each stratum adjusted for [illegible]

[illegible] with an increased risk of any fracture (RR = 1.8 [95% CI, 1.1–3.0]) in the subset of [illegible]

RR = 2.1 (p < 0.05) in women in the lowest fourth of the baseline distribution of [illegible] in the lowest fifth of [illegible] risk factors were [illegible] after [illegible] for [illegible] and [illegible] and [illegible] for [illegible] and [illegible] for obese and African American women

Current smokers had an increased risk for a hip fracture (OR = 1.69 [95% CI, 1.1–2.5]); the OR for a fracture was not significantly higher among former smokers (OR = 1.15 [95% CI, 0.97–1.37])

Table 6.20 Studies on the association between smoking and the risk of fractures at sites other than the hip in men and women

Study	Design	Population
	Vertebral fracture	
Aloia et al. 1985	Age-matched case-control	58 cases 58 controls Volunteer women Mean age 64 years United States
[illegible] et al. 1986	Case-control	208 cases 208 controls Postmenopausal women in the west-central United States Aged 45–79 years United States
Cooper et al. 1989	Surveys, current practice patients	1,002 women Aged 68–93 years Dubbo, Australia 79 fractures
Sanders et al. 1990	Population-based cohort	47,378 men Aged 65 years Black and [illegible]
Scane et al. 1991	Case-control	[illegible] Postmenopausal women Aged 23–76 years (mean age 64) Dorset, England
Daniell et al. 1992	Cohort study	185 consecutive postmenopausal Caucasian women Aged 50–79 years
	Clinical Colles fracture	
Willett et al. 1987	Population-based case-control	584 cases 584 controls Aged 50–74 years United States
Nilsen et al. 1992	Cohort	11,034 women Aged 20–59 years United States 172 fractures over 2.2 years (mean)

[illegible] = Relative risk
[illegible] = Confidence interval.
[illegible] = Body mass index.
[illegible] = Odds ratio.

Findings

Percentage of smokers ([illegible] p <0.01)
Cases: 17.5%
Controls: 11.8%

[illegible] of fracture among [illegible]
[illegible]
Cases: 17.5%
Controls: 11.8%

[illegible] smoking [illegible] years was associated with a [illegible] risk for fracture

RR = 1.1 (95% CI, 0.1–2.0) for current smokers adjusted for age, [illegible] fracture, [illegible] [illegible] and [illegible]

Current smoking was associated with a significantly increased risk of a vertebral fracture (RR = 2.8 [95% CI, 1.2–6.2])

Heavy smoking was a significant risk factor for a vertebral fracture (RR = 3.9 [95% CI, 1.3–12.2])

There was a higher fracture risk in women smokers using estrogen

RR = 1.9 (95% CI, 1.0–3.8) for current smokers (13 cigarettes/day) compared with [illegible]

Table 6.20 Continued

Study	Design	Population
	Distal forearm fracture	
Kreiger et al. 1992	Hospital case-control	Aged 50–84 years Canada 54 fractures
Mallmin et al. 1994	Population-based case-control	186 cases 365 controls Aged 40–59 years Sweden
Honkanen et al. 1995	Retrospective survey	12,766 women Aged 47–58 years Finland 210 fractures
Kato et al. 2000	Prospective cohort	6,208 postmenopausal Japanese women aged 40–79 years at enrollment, average 7.6 years follow-up
	Proximal humerus fracture	
Kelsey et al. 1989	Cohort	1,794 women Aged [illegible] years United States 39 fractures over 2.5 years (mean)
	Ankle fracture	
Sanders et al. 1990	Cohort	1,734 women Aged ≥65 years [illegible] fractures over 3.0 years (mean)
Honkanen et al. 1995	Retrospective survey	12,766 women Aged 47–58 years Finland 210 fractures
	Foot fracture	
Seely et al. 1990	Cohort	9,704 women Aged ≥65 years 204 fractures over 5.0 years (mean)
	Nonhip fractures	
Jacqmin-Gadda et al. 1998	Cohort	1,216 French men and women aged [illegible] years (mean age [illegible]); during a 5-year follow-up, 164 persons (8 [illegible] reported 1 fracture, 19 (0.6%) reported 2 fractures, and 1 (0.03%) reported 3 fractures

[illegible] = Body mass index.

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Findings

RR = 1.5 (95% CI, 0.9–2.6) for current smokers compared with former smokers or never smokers; adjusted for age and BMI

RR = 1.2 (95% CI, 0.9–1.6) for current smokers (10 cigarettes/day)

There was no association with current smoking

There was no association with current smoking

Current smoking was associated with a higher risk for nonhip fractures (OR = 1.68 [95% CI, 1.05–2.80]), but not for hip fractures (OR = 0.73 [95% CI, 0.24–2.20])

Dental Diseases

Diseases of the teeth and their supporting structures are a major public health issue with a significant impact on personal well-being. More than $50 billion were spent on oral health care in the United States in 2000, and each year acute oral conditions result in an estimated 1.6 million missed school days and 2.4 million lost workdays. Although there have been tremendous improvements in the oral health of the U.S. public during the past several decades, oral diseases and conditions remain highly prevalent. For example, recent national data indicate that 68 percent of persons aged 13 through 17 years and 84 percent of those aged 18 years and older have experienced dental caries in their permanent teeth (USDHHS 2000).

As the oral cavity is the first part of the human anatomy to be exposed to mainstream smoke in active smokers, researchers have long hypothesized that smoking could have a deleterious effect on the teeth and their supporting structures. However, research on this association was hampered for decades by (1) lack of consensus on case definitions for some diseases; (2) difficulty in measuring oral conditions and consequent use of indices of questionable validity; (3) some incorrect assumptions about disease etiology, pathogenesis, distribution, and natural history; and (4) limited capacity for epidemiologic investigations within the dental research community. As a result, until recently the literature was sparse and findings were not definitive.

Conclusions of Previous Surgeon General's Reports

The previous Surgeon General's reports on smoking and health did not include dental or periodontal effects of smoking, although oral cancer and related premalignant lesions have been addressed. During the past 15 years, however, there has been a substantial amount of research on smoking and oral health, and this topic was addressed in *Oral Health in America: A Report of the Surgeon General* (USDHHS 2000). This section reviews the epidemiologic evidence for smoking as a causal factor for the most common forms of nonmalignant oral disease; cancers of the oral cavity are covered in Chapter 2.

Periodontitis

The periodontium includes those hard and soft tissue structures that support the teeth: the gingiva, the cementum covering the root surfaces of the teeth, the periodontal ligament that attaches the tooth root surfaces to the adjacent alveolar bone supporting each tooth, and the alveolar bone. The gingiva covers the other periodontal structures and comprises attached and free gingiva. The attached gingiva extends from the bottom of the gingival sulcus to the mucogingival junction, where it is contiguous with the mucous membrane of the lip, cheek, and floor of the mouth. The free gingiva extends from the base of the gingival sulcus to the gingival margin.

In a healthy state, the gingival margin is approximately 0.5 to 2.5 mm coronal to the cemento-enamel junction (CEJ) (where the enamel on the crown of the tooth meets the root). The sulcus is 1 to 3 mm in depth and does not bleed when probed. The base of the sulcus is formed by the junctional epithelium, which joins the gingival connective tissue to the tooth surface. Healthy gingiva is usually pink in color, is well adapted to the teeth, has a stippled surface texture, and is tightly bound to the underlying alveolar bone and the roots of the teeth.

Based on the most recent classification system developed by the American Academy of Periodontology, there are at least eight categories of periodontal diseases and conditions (Armitage 1999). Of these, the two most common are gingivitis and chronic periodontitis. Gingivitis is defined as an inflammation of the gingiva in which the junctional epithelium remains on or near the enamel covering the crown of the tooth. It is characterized clinically by redness, gingival bleeding, edema or enlargement, and occasional gingival sensitivity and tenderness (Genco 1990a). Chronic periodontitis (previously called adult periodontitis) is an inflammation of the gingiva and the adjacent attachment apparatus that is characterized by loss of clinical attachment because of destruction of the periodontal ligament and loss of the adjacent supporting bone (Flemmig 1999). Clinical features of chronic periodontitis may include edema, erythema, gingival bleeding upon probing, periodontal pocketing, or suppuration.

The most common forms of both gingivitis and periodontitis involve bacterial infection. Severe forms of periodontitis often are associated with infection by specific bacteria that colonize the subgingival area (Genco 2000). Destruction of soft tissue and alveolar bone is thought to involve toxins and proteases produced by the bacteria as well as hyperresponsiveness and reactivity of various components of the immune system (e.g., the production of cytokines and prostaglandins). Smoking may play a role in the pathogenesis of periodontal diseases by altering immune function and tissue repair.

The understanding of the distribution and natural history of periodontitis has evolved over the past several decades. Previously, it was thought that virtually all persons were susceptible to severe disease if oral hygiene was inadequate. The disease was considered to progress in a linear fashion throughout life from gingivitis to periodontitis to bone loss to tooth loss, generally attacking the entire dentition and was nearly universal among adults (World Health Organization 1981). This concept was driven, in part, by epidemiologic indices that incorporated signs of both gingivitis and periodontitis, analytic methods that aggregated and averaged measurements within persons and populations, and assumptions about disease progression on the part of the early oral epidemiologists. In the current model of periodontal diseases, a small proportion of persons in most populations are considered to have severe periodontitis; periodontitis is usually preceded by gingivitis but few sites with gingivitis later develop periodontitis; periodontal tissues can undergo some degree of self-repair; and generalized forms of periodontitis are uncommon (American Academy of Periodontology 1996; Burt and Eklund 1999).

Based on current concepts of periodontitis, clinical or epidemiologic assessment of the disease involves detailed measurements of various signs of soft tissue or bone destruction at two to six sites per tooth either on all teeth or on selected teeth. Among the most common measurements is probing pocket depth (PPD), which is measured by inserting a calibrated probe into the gingival sulcus and recording the distance in millimeters from the gingival margin to the base of the gingival sulcus (if healthy) or pocket (if diseased). Because the pathogenesis of periodontitis involves destruction of the junctional epithelium at the base of the sulcus, a PPD greater than 4 mm may indicate disease (Genco 1990b). Another common parameter is the clinical attachment level (CAL), which is measured as distance in millimeters from the CEJ to the base of the gingival sulcus or pocket. It is a direct measure of the position of the periodontal epithelial attachment of a tooth relative to its ideal position at the CEJ. Many cross-sectional studies have used the terminology "loss of periodontal attachment" (LPA) to describe this same parameter, although more recent studies tend to reserve the use of the term LPA for longitudinal assessments of change in the CAL between two points in time. The longitudinal change in CAL is sometimes called relative attachment loss, particularly when computer-linked electronic periodontal probes are used to record the measurements from a fixed reference point such as a cusp tip. Examples of all of these parameters and terms are found in the epidemiologic literature on the association between smoking and periodontal destruction. Because periodontal destruction may occur without deep pocket formation, PPD alone will underestimate disease and may not be sufficient as the prime indicator of disease (Gundsjon 1990). Intraoral radiographs have been used to assess alveolar bone loss from periodontitis, but this approach can have low sensitivity and may underestimate true bone loss (Gundsjon 1990; Bickholz and Haustmann 2000; Pepelassi et al. 2000). In addition, radiography often is not logistically feasible or acceptable to examinees during large-scale field epidemiologic studies. At this time, change in the CAL is considered the prime indicator of periodontal destruction.

Biologic Basis

Microbiology

It is possible that cigarette smoking affects periodontal health by altering the quantity or composition of bacterial dental plaque. Although some studies found that smokers had more visible bacterial plaque than nonsmokers (Shelham 1971; Bastiaan and Waite 1978; Lavstedt et al. 1982; Preber and Bergström 1986), many other studies reported no significant differences in mean plaque levels or rates of plaque accumulation (Alexander 1970; Swenson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1998). Cross-sectional differences in plaque levels between smokers and nonsmokers may be due to differences in oral hygiene practices rather than in smoking per se (Preber and Kant 1973; Andrews et al. 1998). However, the presence of specific bacterial species in periodontal plaque may be more important than the quantity of visible plaque and debris on the teeth in the pathogenesis of severe periodontitis (Genco 1996). Some evidence indicates that smokers may be more likely than nonsmokers to harbor specific periodontal pathogens. A study of adults exhibiting a wide range of

periodontal conditions (Zambon et al. 1996) found that subgingival infection with *Bacteroides forsythus* was more common in current smokers even after adjusting for disease severity, with a dose-response relationship between the amount of smoking and infection. Current smokers were also more likely than former or lifetime nonsmokers to have subgingival infection with *Actinobacillus actinomycetemcomitans*. Consistent with those findings, a study of dental clinic patients found that plaque samples from smokers were 11 times more likely than samples from nonsmokers to test positive for one of three periodontal pathogens (Kazor et al. 1998). In a study of young adults with early-onset periodontitis (Ramma et al. 1999), 11 postulated periodontal pathogens were detected more frequently and in greater numbers in the subgingival plaque from smokers than from nonsmokers. Smoking may increase the likelihood of infection with periodontal pathogenic microorganisms even among persons with no clinical signs of disease. In a study of young adults who did not have periodontitis (Shiloah et al. 2000), smokers were 18 times more likely than nonsmokers to have at least one of eight periodontal pathogens in their subgingival plaque. Several studies, however, reported no differences in the plaque bacteria between smokers and nonsmokers (Preber et al. 1992; Stoltenberg et al. 1993). Additional evidence suggests that smoking may act synergistically to potentiate the effects of toxins produced by periodontal pathogenic bacteria (Sayers et al. 1999).

Immune Function

There is substantial evidence that smoking affects both localized and systemic components of the immune system, although the links between these effects and periodontal disease remain to be established. Smoking increases the number but impairs the functions of polymorphonuclear leukocytes (PMNs, or neutrophils), peripheral blood cells that represent the first line of defense against microorganisms (Noble and Penny 1975; Barbour et al. 1997). Either an impairment of the PMN's ability to neutralize periodontal infections or an overstimulation of potentially tissue-destructive processes can lead to periodontal destruction (American Academy of Periodontology 1989). For example, smoking can impair PMN chemotaxis, phagocytosis, and oxidative burst (Eichel and Shahrik 1969; Kenney et al. 1977; Ryder et al. 1998). Impaired phagocytosis has been implicated in refractory periodontitis (MacFarlane et al. 1992). Smoking also appears to compromise the function of macrophages, which play a vital role in both humoral and cell-mediated immunity, and of B lymphocytes, the major cell type involved in the humoral immune system. Exposure to cigarette smoke also appears to have an immunosuppressive effect on T lymphocytes, which may reduce antibody response to periodontal bacteria (Barbour et al. 1997). Smokers may have a decreased production of antibodies specific to periodontal pathogens, especially IgG2 (Quinn et al. 1998). Recent evidence suggests that levels of cytokines in gingival crevicular fluid, which are secreted by mononuclear cells and are associated with collagen destruction and bone resorption, may be increased in smokers (Bostrom et al. 1998a,b). Furthermore, there may be a synergistic interaction between smoking and the genotype for a specific cytokine, IL-1, in the development of severe periodontitis (Kornman and di Giovine 1998).

Gingival Blood Flow and Soft Tissue Effects

It has long been hypothesized that the peripheral vasoconstrictive effect of tobacco smoke and nicotine reduces gingival blood flow and thereby impairs the delivery of oxygen and nutrients to gingival tissue. There is some evidence of reduced blood flow in gingival tissues (Clarke et al. 1981; Clarke and Shephard 1984) and reduced size and altered morphology of capillaries in oral mucosa and gingival tissues (Johnson et al. 1989) following exposure to tobacco smoke or nicotine. However, more recent evidence appears contradictory (Raab and Oberg 1987; Johnson et al. 1991). Smokers tend to exhibit less gingival bleeding than nonsmokers, even with control for bacterial plaque levels (Preber and Bergstrom 1985, 1986; Bergström and Preber 1986; Bergström 1990; Danielsen et al. 1990; Newburn 1996). However, this reduced gingival bleeding may be related more to the suppression of an inflammatory response than to reduced gingival blood flow.

Nicotine can be stored in and released from periodontal fibroblasts, possibly affecting their morphology and ability to attach to root surfaces (Raulin et al. 1988; Hanes et al. 1991; James et al. 1999). In addition, nicotine may inhibit the growth of gingival fibroblasts and their production of collagen and fibronectin, components of the gingival extracellular matrix involved in the structure and attachment of gingiva (Tipton and Dabbous 1995). Thus, it is possible that smoking impairs the ability of periodontal tissues to repair damaged junctional epithelium. Smoking impairs

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wound healing and compromises the prognosis following surgical and nonsurgical periodontal therapy (Preber and Bergström 1990; Ah et al. 1994; Newman et al. 1994; Rosenberg and Cutler 1994; Preber et al. 1995; Tonetti et al. 1995; Grossi et al. 1996, 1997; Rakhmil et al. 1996; Kinane and Radvar 1997; Trombelli and Scabbia 1997; Bouttón et al. 1998a; Machtei et al. 1998; Renvert et al. 1998; Palmer et al. 1999; Papapanou-poulos 1999; Soder et al. 1999). One study that employed statistical modeling of longitudinal changes in the CAL concluded that diminished capacity for repair, rather than direct tissue damage, probably was the major mechanism involved in smoking-associated periodontal destruction (Faddy et al. 2000).

Epidemiologic Evidence

Epidemiologic studies of smoking and periodontitis have employed a variety of case definitions for disease, using various combinations of PPD, CAL or LPA, and alveolar bone loss. Some studies used indices for "periodontal disease" that are no longer considered valid indicators for the prevalence of disease in populations (Burt and Eklund 1999). Other studies employed indices that originally were intended for use in population-based treatment planning and not for etiologic studies, such as the Community Periodontal Index of Treatment Needs (Ainamo et al. 1982). Some studies did not use a case definition for disease, but instead assessed mean levels of one or more clinical parameters among exposed and unexposed groups, or described the proportion of the study population that exceeded various measurement thresholds (e.g., ≥4 mm LPA). Some studies, primarily conducted before the 1970s, provided no case definition other than diagnosis by the examiner. Despite the numerous problems measuring the disease, published epidemiologic and clinical studies consistently show a moderate to strong degree of association between smoking and periodontitis.

To identify epidemiologic studies of smoking and periodontitis, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000, using the following Medical Subject Headings (MeSH) key words: "smoking," "tobacco," "periodontal diseases," and "periodontitis." These terms also were searched as title words. The smoking and health database maintained by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, was also searched using those terms as key words. Reference lists from published studies, review articles, and textbooks were examined to identify additional studies.

Tables 6.21 through 6.23 summarize the findings from 6 case-control studies, 52 cross-sectional studies, and 12 cohort studies conducted between 1959 and 2000. The case-control studies consistently found that persons with periodontitis were more likely than controls without periodontitis to be smokers, although not all studies separated current smokers from former smokers in their analyses. These studies generally controlled for potential confounders in either the selection of a control group or in their analyses. Cross-sectional studies that attempted to estimate parameters such as the odds ratio (OR) consistently reported moderate to strong degrees of association between smoking and periodontitis under a wide range of case definitions (Beck et al. 1990; Horning et al. 1992; Haber et al. 1993; Stoltenberg et al. 1993; Grossi et al. 1994, 1995; Sakki et al. 1995; Tomar et al. 1995; Ahlberg et al. 1998; Dolan et al. 1997a; Norderyd and Hugoson 1998; Shimazaki et al. 1998; Wakai et al. 1999; Tomar and Asma 2000). Consistent with the findings from case-control and cross-sectional studies, cohort studies reported RR estimates for smoking and onset or progression of periodontitis of 1.4 to more than 10, using a wide range of outcome measures. Of the cross-sectional studies that examined the relationship separately for current smokers and former smokers, current smokers were more likely than former smokers to have periodontitis (Haber et al. 1993; Dolan et al. 1997a; Wakai et al. 1999; Tomar and Asma 2000). Two case-control studies (Haber and Kent 1992; Gelskey et al. 1998) and several cross-sectional studies (Grossi et al. 1994, 1995; Norderyd and Hugoson 1998; Wakai et al. 1999; Tomar and Asma 2000) reported a significant dose-response relationship between the number of cigarettes smoked per day and disease status. Two of these studies used cigarette-years[a] or pack-years as the measure for exposure (Grossi et al. 1994, 1995), which combined quantity and duration of smoking to characterize the exposure. One study reported a significant dose-response relationship between the duration of smoking and disease risk (Tomar and Asma 2000). That study also found a significant inverse relationship between the number of years since quitting smoking and the odds of having periodontitis.

[a]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Nearly all other reviewed studies reported either mean measures of PPD or CAL/LPA or radiographically demonstrated alveolar bone loss by smoking status, or they reported the percentage of persons with some specified number or percentage of sites exceeding some threshold on one or more of these clinical parameters. With only one exception (Preber et al. 1980), all cross-sectional and cohort studies that measured differences in mean CAL/LPA or mean PPD found a worse periodontal status among smokers than among nonsmokers. That 1980 study (Preber et al. 1980), however, was conducted with young military recruits whose duration of smoking must have been relatively short because of their age.

Evidence Synthesis

The available epidemiologic literature is highly consistent in showing a moderate to strong association between cigarette smoking and periodontal destruction. The association is robust across a wide range of case definitions, populations, and study designs. There is also evidence of a dose-response relationship between smoking intensity and risk for periodontitis. Both number of cigarettes smoked and duration of smoking are positively associated with disease risk. The risk of periodontitis appears to decrease after smokers stop smoking, with a decreasing risk as the duration of successful cessation increases. Although only a few prospective cohort studies have been carried out, they consistently found that smokers were more likely than nonsmokers to experience the onset or progression of disease. The association cannot be explained by confounding.

The mechanisms involved in smoking-associated periodontal destruction are still not fully understood. However, available evidence supports several hypotheses. An immune mechanism is plausible because smoking affects many elements of the human immune system. The effects of smoking on local and systemic immune factors may make the smoker more susceptible to bacterial infection. In addition, substantial evidence indicates that smoking impairs the regeneration and repair of periodontal tissues. The evidence is inconsistent in suggesting that smoking quantitatively or qualitatively alters the microflora of subgingival plaque.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

Implications

Smoking intervention should be a major component of prevention and treatment of periodontitis. A recent study (Tomar and Asma 2000) concluded that more than 50 percent of the cases of adult periodontitis in the United States are attributable to cigarette smoking. In light of this conclusion, and because more than one-half of U.S. adult smokers visit a dentist each year (Tomar et al. 1998), the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit. The dental office may also provide an opportune setting for tobacco use prevention efforts among young people (Howell et al. 1998). Unfortunately, a lack of awareness and inadequate skills may be barriers to further involvement by dentists and dental hygienists (Secker-Walker et al. 1994; Dolan et al. 1997b).

Further research is needed to achieve a greater understanding of the mechanisms involved in smoking-associated periodontitis. In addition, more behavioral research is needed to enhance the willingness and ability of dentists and dental hygienists to intervene in their patients' use of tobacco and to counsel younger patients against tobacco use. Educational research should identify effective methods for training students of dentistry and dental hygiene, as well as licensed clinicians, to become competent at counseling their patients to stop using tobacco and assisting patients who want to quit (Tomar et al. 1998; Barker and Williams 1999; Cubana et al. 1999).

Dental Caries

Dental caries is an infectious, communicable, multifactorial disease in which bacterially produced acids dissolve the hard enamel surface of a tooth (Featherstone 1999). Unchecked, the bacteria may then penetrate the underlying dentin and progress into the soft pulp tissue, which is rich in blood and nerve tissue. Dental caries commonly results in loss of tooth structure and discomfort. Untreated dental caries commonly progresses to incapacitating pain and a bacterial infection that leads to pulpal necrosis, tooth extraction, and loss of dental function, and can progress to an acute systemic infection. The major etiologic factors for this disease are thought to be specific bacteria in dental plaque (particularly *Streptococcus [S.] mutans* and *S. lactobacilli*) on susceptible tooth surfaces and the availability of fermentable carbohydrates.

Most epidemiologic studies conducted during the past 60 years have used some variation of the decayed, missing (due to caries), or filled permanent teeth (DMFT) index (Klein et al. 1938) to measure the frequency of dental caries. Until the mid-1980s the proportion of the population with dental caries was rarely used to estimate disease prevalence in industrialized populations because the disease was nearly universal. The DMFT index is more a measure of disease severity than of disease prevalence: it is simply the sum of the number of permanent teeth (T) that are decayed (D), missing due to dental caries (M), or filled (F). This index, if applied to the number of coronal (i.e., enamel-covered) tooth surfaces (S), is designated the DMFS. The M component is often omitted in adult studies because of the inherent uncertainty as to why a tooth is missing. Thus, some studies report DFT or DFS scores. Other studies report the components of DMFT individually, such as DS, FS, and MS. Nearly all studies aggregate DMF data by reporting the population mean. The number of root surfaces affected by caries is almost always scored and reported separately from coronal caries, and usually is designated as RDFS or RDS (the M component is not reported for root-surface caries).

Biologic Basis

There are several hypothesized mechanisms that may underlie the association between smoking and dental caries. As discussed in the section on smoking and periodontitis, evidence is inconsistent in showing that smoking per se alters either the bacterial profile in the gingivi or the rate of formation of dental plaque (Alexander 1970; Svensson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1988). Differences in oral care behavior between smokers and nonsmokers provide an indirect explanation. Perhaps the most consistent explanation is that smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Preber and Kant 1973; Macgregor and Rugg-Gunn 1986; Andrews et al. 1996).

Several studies concluded that smoking might lower the pH or reduce the buffering capacity of saliva (Heintze 1984; Parvinen 1984), impairing the function of saliva as a protective factor against enamel demineralization (Edgar and Higham 1995). In contrast, one review concluded that smoking increases salivary flow rate (Macgregor 1989), raising pH and increasing salivary calcium concentration (ten Cate 1996). These factors would tend to favor enamel remineralization but benefit would come only if the flow rate increase were sustained. Another comprehensive review concluded that smoking has a minor effect on saliva flow rate and its chemical composition, at least in terms of factors thought to affect dental cariogenesis (Christen et al. 1991). In sum, an effect of smoking on salivary function does not appear to be a key mechanism in causing dental caries.

The association between smoking and root-surface caries suggested by several studies may be due, in part, to the periodontal effects of smoking. The loss of periodontal attachment and subsequent exposure of root surfaces are necessary conditions for root-surface caries to occur (Burt et al. 1988; Stamm et al. 1990). Persons who experience a loss of periodontal attachment attributable to smoking may also be at greater risk for subsequent root-surface caries.

Epidemiologic Evidence

To identify the epidemiologic studies on smoking and dental caries, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000. The following MeSH key words were used: "smoking," "tobacco," "dental caries," and "tooth demineralization." These terms also were searched as title words. The smoking and health database maintained by CDC's Office on Smoking and Health was also searched using the same terms as key words. Reference lists from published studies, review articles, and textbooks were sources for additional studies.

Table 6.24 summarizes 12 cross-sectional studies and 3 cohort studies published between 1952 and 1999. Most cross-sectional studies used some variation of the DMF index to measure caries prevalence: all but two (Hart et al. 1985; Tomar and Winn 1999) found that smokers experienced more coronal dental caries than nonsmokers, as measured by mean DS, DFS, DMFS, or DMFT. In general, differences between smokers and nonsmokers in mean DMFT or DMFS were small, even in studies in which the differences were reported to be "statistically significant." The largest differences in numbers of carious lesions were reported in studies that used DMFS (Ludwick and Massler 1952; Ainamo 1971; Zitterbart et al. 1990; Axelsson et al. 1998). None of those studies, however, appeared to limit the "missing" component of DMFS to those tooth surfaces lost due to caries. Consequently, these studies may mix caries caused by smoking with the advanced periodontal destruction that can cause tooth loss in adults.

Few of the studies on the association between smoking and dental caries controlled for potential confounding factors. Although the observed association between smoking and dental caries may reflect a causal relationship, it is also possible that it reflects factors common to both smoking and the risk of dental caries. For example, in industrialized nations both dental caries (USDHHS 2000) and cigarette smoking (Giovino et al. 1985) are more prevalent among groups with lower socioeconomic status (SES) than among higher SES groups. SES is a strong correlate of factors that affect dental caries status, such as diet, use of dental services, and oral hygiene practices (USDHHS 2000). None of the studies adjusted for SES or other potential confounding factors in examining the association between smoking and dental caries. Several literature reviews do suggest that the association between smoking and dental caries may reflect the tendency for smokers to practice less effective dental hygiene and plaque removal (Macgregor 1989; Christen et al. 1991; Kassirer 1994; Andrews et al. 1996).

Few studies adjusted for other notable correlates of both smoking and dental caries in their analyses. The DMF index is a cumulative, irreversible index. As persons experience decayed or filled permanent tooth surfaces or lose teeth over their lifetimes, their DMFT or DMFS scores will increase. Therefore, DMFT and DMFS can be associated strongly with age even if age per se is not a risk factor for incidence of dental caries. Few studies, however, adjusted for age in their analyses. Several studies provided age-specific mean caries scores (Ludwick and Massler 1952; Zitterbart et al. 1990; Axelsson et al. 1998) or age-specific significance testing of differences in means (Hirsch et al. 1991), which revealed an inconsistent association between smoking and caries within age groups. In the one study that used a nationally representative sample of U.S. adults and adjusted for age and race or ethnicity, DFT and DMS were actually slightly lower among male smokers than among those who had never used tobacco (Tomar and Winn 1999).

Two studies attempted to investigate a dose-response relationship between smoking and dental caries (Ludwick and Massler 1952; Ainamo 1971). Although smokers in the highest category of cigarettes smoked per day had experienced slightly higher DMFT, DMFS, or DS than those in the lowest dose categories, the relationship was not consistent. The first study presented age-specific comparisons of mean DMFT and DMFS by the number of cigarettes smoked per day, which showed no clear pattern within age strata. The second study did not present age-stratified or age-adjusted estimates, which potentially could present difficulties in interpreting the association between a disease index that is cumulative with age and an exposure that probably was increasing with age in the study population (aged 16 through 26 years).

Smoking may be associated more with root-surface caries than with coronal caries. Two cohort studies (Ravald et al. 1993; Locker 1996) and two cross-sectional studies (Locker 1992; Tomar and Winn 1999) reported higher mean RDFS or RDS scores among smokers, but in one cohort study (Locker 1996) smoking was not found to be a significant predictor of root-surface caries in multiple logistic regression modeling.

Evidence Synthesis

Few studies have investigated the association between cigarette smoking and dental caries. The available literature is fairly consistent in suggesting that smokers may experience slightly more decayed, missing, or filled coronal tooth surfaces. In addition, smokers generally experienced more decayed or filled root surfaces than nonsmokers. However, many of the published studies did not address potential confounders of these associations. It is therefore possible that the observed associations could reflect in part the presence of other factors associated with both smoking and dental caries. Evidence for a dose-response relationship is sparse and inconsistent. Studies that examined whether quitting smoking reduced the risk of caries development were not identified.

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There is little evidence for a biologic mechanism that would explain the role of smoking in the development of coronal dental caries. Methodologic considerations limit the interpretation of findings from epidemiologic studies. The few lines of investigation undertaken have been inconsistent in identifying either bacterial or salivary effects that would be expected to increase this risk.

Some evidence suggests that smoking may indirectly increase the risk for root-surface caries. The mechanism probably involves an increased exposure of root surfaces of teeth secondary to loss of periodontal attachment. This relationship *may reflect the impact* of smoking on periodontium and the subsequent exposure of tooth root surfaces to the oral environment.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Implications

To better characterize the relationship between cigarette smoking and dental caries, future investigations will need to control for potential confounding factors. These studies should be of the cohort design to allow for assessments of the effect of smoking on carious lesion formation and to determine whether smoking cessation reduces disease incidence. Investigations into an association between smoking and root-surface caries will need to apply indices that take into account the number of root surfaces at risk, such as the Root Caries Index (Katz 1980), or control for root surface exposure in trying to identify whether smoking acts through a direct or indirect mechanism.

The increased risk for root-surface caries may be due to smoking-associated periodontal destruction and subsequent exposure of root surfaces of teeth to the oral environment. Because of the causal relationship between smoking and periodontitis as well as with many other diseases, and because more than one-half of U.S. adult smokers visit a dentist each year, the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit.

Table 6.21 Case-control studies on the association between smoking and periodontitis

Study	Number of cases/ controls	Case definition	Sources of cases/ controls	Findings: Smoking status	Findings: Odds ratio	Findings: 95% confidence interval
Preber and Bergström 1986	260/ 1,769	Moderate to severe periodontitis; advanced periodontitis (mean PPD* >4.5 mm)	Dental school periodontal clinic/ population-based sample	Current smokers		
				Moderate to severe periodontitis	2.1	1.7–2.7
				Advanced periodontitis	2.4	1.7–3.5
Bergström and Eliasson 1987b	230[a]	PPD of 6 mm or greater	Periodontal patients/ population-based sample	Current smokers		
				Men	2.8[a]	NR[b]
				Women	2.1[a]	NR
				Total	2.5[a]	NR
Haber and Kent 1992	186/208	Moderate periodontitis (20–50% bone loss on ≥1 surface); advanced periodontitis (>50% bone loss on ≥1 surface)	Periodontal offices/general dental practices	Current smokers		
				Extent of bone loss		
				Index rate in advanced cases	2.6	1.6–3.9
				Current smokers (matched controls)	3.3	1.8–5.8
				Amount of alveolar bone loss		
				≤1/3 (mild)	1.0	0.4–2.5
				>1/3 to 2/3 (moderate)	5.4	2.8–10.6
				>2/3 (severe)	3.3	0.2–6.5
				Men	4.5	1.6–12.1
				Women	1.8	0.9–3.7
				All	3.1	2.0–12.4
McTigue et al. 1994	317/ [illegible]	Earliest age periodontitis needs medical or conventional treatment (called for regression analysis)	Private periodontal practices; persons over 60 of dental grading of periodontal tissues; total number of persons	Current smokers (odds ratio estimates from multivariate regression analysis; 95% confidence intervals; 3 smokers in the <60 group)	2.1[b]	0.8–4.4
						2.0–[illegible]

*PPD = Probing pocket depth.
[a]Odds ratio estimates in this study were based on comparisons with smoking prevalence in a general population survey in Stockholm, Sweden. However, periodontal health was not examined in this "control" group.
[b]NR = Data were not reported.

Table 6.21 Continued

Study	Number of cases/ controls	Case definition	Sources of cases/ controls	Findings: Smoking status	Findings: Odds ratio	Findings: 95% confidence interval
Gelskey et al. 1998	205/205	≥1 tooth with alveolar bone loss >3 mm, or ≥1 tooth with PPD* ≥7 mm	Dental school clinic	Never smoked	1.0	NR
				Ever smoked	1.8	1.1–2.9
				Cigarette-years[a]		
				Aged 35–87 years		
				1–300	*1.2*	*0.7–1.8*
				301–500	1.8	0.9–2.7
				>500	3.8	2.9–4.7
				Aged 35–54 years		
				1–300	1.0	0.3–1.7
				301–500	3.2	2.1–4.2
				>500	4.3	6.2–8.5
				Aged 55–87 years		
				1–300	*1.7*	*0.7–3.9*
				301–500	1.1	0.01–4.0
				>500	2.2	0.01–7.8
Tezuka et al. 1994	200/197	≥2 teeth with loss of periodontal attachment and ≥1 tooth	Clinical [illegible] [illegible] for periodontal diseases	Males		
				Former smokers	1.0	NR
				Current smokers	2.1[b]	0.9–5.1
				Females		
				Former smokers	1.0	NR
				Current smokers	4.0[b]	2.1–7.6

*PPD = Probing pocket depth.
[a]Cigarette-years = Number of years of smoking multiplied by the number of cigarettes smoked per day.
[b]Crude odds ratio estimates were calculated from data reported in the paper.

Table 6.22 Cross-sectional studies on the association between smoking and periodontitis

Study	Population	Findings	Comments
Arno et al. 1959	728 male factory workers and staff Aged 21–45 years Norway	No quantitative results were reported	Mean alveolar bone loss appeared to increase with more cigarettes/day in graphic plots of deviations from the sample mean; the analysis of variance verified with a significant degree of confidence that the different [illegible] could be due to chance (mean and test scores were not reported)
Brandtzaeg and Kleinbeg 1964	240 male army recruits Aged 18–20 years Norway	Mean Debris and Calculus Index scores Nonsmokers 0.72 ≤10 cigarettes/day 0.79 ≥10 cigarettes/day 1.02 Mean Oral Hygiene Index scores Nonsmokers 1.22 ≤10 cigarettes/day 1.45 ≥10 cigarettes/day 1.63	Authors concluded that there was a significant correlation between smoking habits and the Periodontal Index scores, but statistical significance was not reported
Solomon et al. 1968	2,182 male and 1,095 female dental and hospital patients Aged 20–79 years United States (New York)	Periodontal [illegible] clinical diseases were evaluated by physicians using examinations and questionnaires. Statistically significant [illegible] [illegible] were found between smoking and periodontal disease in males aged 40 years and older, and in females aged 50 years and older	Periodontal disease was based on both gingival recession and periodontal pocket formation; smoking was strongly associated with periodontal disease in the age-standardized Cochran's test for both males and women
Sumariwalla and Osterman 1969	Probability sample of 1,474 men and 1,501 women Aged 25 years (mean) at entry to study	Multivariate analysis of Periodontal Index scores and the Periodontal Disease Index were significantly related to cigarette smoking Men 0.55 Women 0.56	The Periodontal Disease Index was used to estimate the relationship between current smoking (cigarettes per day) and periodontal disease; the results of Pearson correlation coefficients [illegible] [illegible]
Ainamo 1971	167 male military recruits Aged 18–26 years Finland	Mean LPA* by CPI* smoking habit Cigarettes/day — LPA 0 — 0.049 1–9 — 0.062 10–20 — 0.072 >20 — 0.108	LPA was measured clinically on 4 surfaces of all erupted teeth

Note: Unless otherwise defined, current, former, and never refer to smoking status.
*LPA = Loss of periodontal attachment.

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Table 6.22 Continued

Study	Population	Findings	Comments
Preber et al. 1980	164 male army conscripts Aged 19–27 years Sweden	There were no significant differences between smokers (n = 81) and nonsmokers (n = 53) in mean bone level or PPD[1]	PPD was clinically assessed on 6 teeth (1st molars, upper right central incisor, lower left central incisor); radiographic assessments were of lower incisors only
Bergström and Eliasson 1983	[illegible]	Mean alveolar bone index High exposed teeth 0.69 Low exposed teeth 0.94 Number of [illegible] High exposed teeth 11.2 Low exposed teeth 9.7	After [illegible] radiographic [illegible] number of [illegible] teeth [illegible]
Feldstein et al. 1983	100 men Mean age of nonsmokers = 47.9 years; mean age of smokers = 43.8 years United States	Mean PPD[1] (mm) Smokers 0.73 Nonsmokers 0.56 Mean bone loss Smokers 0.70 Nonsmokers 0.42	Adjusted for age in the analysis of variance; the nonsmoking group included former smokers
Lavstedt et al. 1983	Population-based sample of 2,345 persons Aged 25–74 years Under 3 Extra	Mean periodontal [illegible] score by smoking status Current smokers [illegible] Former smokers 1.1 Never smokers 1.0	[illegible] adjusted [illegible] socioeconomic [illegible] poverty path [illegible] group [illegible]

[1]PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments
Markkanen et al. 1985	Population-based sample of 2,019 men and 2,349 women Aged ≥30 years Finland	Prevalence (%) of PPD[1] 4–6 mm Men Current smokers 51.6 Nonsmokers 51.7 Women Current smokers 50.8 Nonsmokers 50.8 Total Current smokers 51.3 Nonsmokers 51.2 Prevalence of PPD >6 mm Men Current smokers 38.1 Nonsmokers [illegible] Women Current smokers [illegible] Nonsmokers [illegible] Total Current smokers [illegible] Nonsmokers 21.1	Nonsmokers included former smokers; periodontal status was measured by the Periodontal Treatment Need System (PTNS), classifying each quadrant of the mouth by the highest score within that quadrant and each person according to the highest quadrant score; there were no significant differences between smokers and nonsmokers in periodontal pocketing when stratified by gender; smoking was not a significant correlate of the PTNS score in a log-linear model that also included gender, age, and the number of dentate quadrants
Bergström and Eliasson 1987a	300 male and 53 female professional musicians Aged 21–60 years Sweden	Mean [illegible] probing depth (mm) Aged 21–40 years Smokers [illegible] Nonsmokers [illegible] Aged 41–60 years Smokers [illegible] Nonsmokers [illegible] Total Smokers [illegible] Nonsmokers [illegible]	Both gender and [illegible] were significantly associated with [illegible] than in nonsmokers in each age group and plaque index score; there were no significant differences [illegible] Smokers, former smokers were combined [illegible]
Bergström and Eliasson 1987b	208 male and 34 female professional musicians Aged 21–60 years Sweden	Mean number of periodontal pockets ≥4 mm Aged 21–40 years Smokers 27.3 Nonsmokers 13.4 Aged 41–60 years Smokers 39.9 Nonsmokers 31.0 Total Smokers 36.0 Nonsmokers 21.8	The mean number of periodontal pockets was significantly greater in smokers than in nonsmokers across age groups and plaque index scores

[1]PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments
Levy et al. 1987	Population-based sample of 477 dentate adults Aged ≥65 years United States (Iowa)	Multiple linear regression coefficient for proportion of teeth that were periodontally healthy by the number of cigarettes smoked Males -0.002 Females -0.008 (not statistically significant)	Periodontally healthy teeth were defined as PPD[1] ≤3 mm with no gingival bleeding; other variables in the models for males were the number of teeth, age, Parkinson's disease, ever smoked a pipe, exercise level, and proportion of teeth with calculus [illegible] with regression for females the number of teeth, age [illegible] ration of teeth with [illegible] ray, [illegible] m
Beck et al. 1988	Population-based [illegible] of 681 blacks and 1,256 whites Aged ≥65 years Durham County, North Carolina	Odds ratios [illegible] CI[3] for [illegible] were [illegible] Whites Unadjusted [illegible] Adjusted 6.2 (2.6–14.5) Blacks Unadjusted 2.8 (1.4–5.7) Adjusted 2.9 (1.6–5.1)	Severe [illegible] periodontal [illegible] form and PPD ≥4 mm [illegible] assessed [illegible] reported [illegible] between [illegible] smoking [illegible] Farmer et al.

[1]LBA = Loss of periodontal attachment.
[2]PPD = Probing pocket depth.
[3]OR = Odds ratio.
[4]CI = Confidence interval.

Table 6.22 Continued

Study	Population	Findings	Comments
Goultschin et al. 1990	154 male and 190 female hospital workers Aged 17–74 years Israel	Mean number of sextants affected, based on CPITN[2] scores 0 Smokers 0.32 Nonsmokers 0.84 1 Smokers 0.55 Nonsmokers 1.01 2 Smokers 1.52 Nonsmokers [illegible] 3 Smokers 2.48 Nonsmokers 1.71 4 Smokers [illegible] Nonsmokers [illegible]	The mean number of affected sextants did not differ significantly between smokers and nonsmokers for CPITN scores 2 and 4; adjusted for age and gender
Hansen et al. 1988a	[illegible]	[illegible]	Does not differentiate [illegible] current smokers [illegible]
Bergström et al. 1991	210 female dental hygienists Aged 24–60 years Sweden	Mean alveolar bone loss (mm) Current smokers 1.71 Former smokers Never smoked Mean alveolar bone loss (mm) in current smokers by cigarettes/day ≤10 1.80 >10 [illegible] Mean alveolar bone loss (mm) in current smokers by duration of smoking (years) ≤15 1.59 >15 1.84	Bone loss was assessed radiographically for [illegible] septum of right [illegible] associations between bone [illegible] and cigarette habits were consistent within age strata; smoking was a significant predictor of bone loss in multiple linear regression models that included age
Hirsch et al. 1991a	1,926 men and 2,063 female civil servants United States	OR (95% CI) for [illegible] of [illegible] periodontitis [illegible] smokers 1.9 (1.2–2.7)	[illegible] regression [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]

[1]LBA = Loss of periodontal attachment.
[2]CPITN = Community Periodontal Index of Treatment Needs.

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Table 6.22 Continued

Study	Population	Findings	Comments
Locker 1992; Locker and Leake 1993	Population-based sample of 702 dentate adults Aged ≥50 years Canada (Ontario)	Mean LPA[a] (mm) Current smokers 3.7 Former smokers 2.9 Never smoked 2.7 Sites (%) with LPA ≥2 mm Current smokers 84.7 Former smokers 77.6 Never smoked 72.3 Sites (%) with LPA ≥3 mm Current smokers 30.2 Former smokers 15.9 Never smoked 13.8 Prevalence of severe LPA Current smokers [illegible] Former smokers [illegible] Never smoked [illegible]	Severe LPA was defined as the upper 20th percentile of distribution of LPA in the full study population (≥3.8 mm)
Haber et al. 1993	[illegible]	[illegible]	[illegible]
Stoltenberg et al. 1993	65 [illegible] pairs (mean age 48 years) and 126 nonsmokers (mean age 49 years) matched for age, gender, and plaque and calculus levels HMO patients United States (Minnesota)	Mean PPD[b] (mm) Smokers 3.12 Nonsmokers 2.94 Prevalence (%), OR, and 95% CI for having mean PPD ≥3.5 mm Smokers 24 5.3 (2.0 13.8) Nonsmokers 6 (referent) Prevalence (%) of ≥1 site with PPD ≥3.5 mm Smokers 76.2 Nonsmokers 59.5	It is unclear if former smokers were included in the study; smokers also had a higher prevalence than nonsmokers of ≥1 site with PPD ≥4.0 mm or ≥5.5 mm

[a]LPA = Loss of periodontal attachment.
[b]PPD = Probing pocket depth.
[c]HMO = Health maintenance organization.

Table 6.22 Continued

Study	Population	Findings	Comments
Wouters et al. 1993	Population-based sample of 378 men and 345 women Aged ≥20 years Sweden	Age-standardized mean interproximal alveolar bone height as a percentage of root length, by smoking status Current smokers 77.0 Former smokers 81.5 Never smoked 83.1	Current smoking (but not former smoking) was significantly associated with mean interproximal alveolar bone heights in a multiple linear regression model that included gender, age, urban/rural residence, level of education, [illegible] dental and dental h[illegible]s, number of tooth surf[illegible]ape and calculus score[illegible] the presence of [illegible]
[illegible] et al. 1994	Population-based sample of 741 women and 565 men Aged 25–74 years United States Cuba	OR (95% CI) for smoking and LPA[a] Pack-years** [illegible] 2.05 (1.47–2.87) [illegible] 3.47 (2.19–4.85) [illegible] 4.31 (2.26–8.35)	[illegible] [illegible] [illegible] [illegible] [illegible] estimates [illegible] status [illegible] [illegible] [illegible]
Linden and Mullally 1994	Random sample of 82 regular dental attenders Aged 20–33 years Northern Ireland	Mean PPD[b] (mm) Current smokers 2.9 Nonsmokers 2.6 Mean number of pockets ≥4 mm Current smokers 14.6 Nonsmokers 5.6 Mean LPA (mm) Current smokers 1.2 Nonsmokers 0.7 Mean number of LPA sites ≥2 mm Current smokers 21.8 Nonsmokers 9.3	Nonsmokers examined were smokers and those who had quit ≥2 years before examination

[a]LPA = Loss of periodontal attachment.
[b]PPD = Probing pocket depth.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day

Table 6.22 Continued

Study	Population	Findings	Comments
Söder et al. 1994	Population-based sample of 840 men and 841 women Aged 31–40 years Sweden	Prevalence (%) of teeth (≥1) with PPD[b] ≥5 mm by smoking status Current smokers 23.1 Former smokers 18.7 Never smoked 10.1 Mean number (%) of teeth with PPD ≥5 mm by smoking status Current smokers [illegible] Former smokers [illegible] Never smoked [illegible]	Smoking was a highly significant correlate of the number of teeth with PPD ≥5 mm in a multiple linear regression model that also included gender, most recent dental visit, debris and calculus index scores, and the number of teeth
Grossi et al. 1995	Population-based sample of 506 women and 665 men Aged 25–74 years United States Cuba	OR (95% CI) for smoking and [illegible] Pack-years [illegible] 2.18 (1.52–3.14) [illegible] 3.25 (2.28–4.64) [illegible] 3.79 (1.85–8.27) [illegible] 3.26 (0.94–13.23)	[illegible] [illegible] [illegible] [illegible] [illegible]

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Table 6.22 Continued

Study	Population	Findings	Comments
Tomar et al. 1995	416 male and 58 female HIV[b]-infected military personnel Aged 18–40 years United States	Unadjusted OR (95% CI) for having ≥1 LPA[a] site ≥5 mm Current smokers 2.6 (1.5–4.8) Former smokers 2.1 (1.2–4.9) Never smoked 1.0 (referent) Adjusted OR (95% CI) for having ≥1 LPA site ≥5 mm Current smokers 2.1 (1.1–4.3) Former smokers 1.0 (referent)	This multiple logistic regression model included age, stage of HIV disease, gender, retirement status, gingival cratering or ulceration, AZT[c] use, and the presence of oral candidiasis
Alabaster et al. 1988	145 men (universal screening) Aged 18–69 years Veterans	Adjusted OR (95% CI) for having LPD[1] ≥4 mm Smokers 2.1 (1.1–3.9)	Used the CPITN[2] (severity with [illegible] smoking, oral hygiene, [illegible] gingival others were [illegible] in the logistic [illegible] model included [illegible] presence of calculus, [illegible] 500 Hemoglobin [illegible] total protein, dental [illegible] age
Grossman et al. 1988	[illegible] male [illegible] aging [illegible] years [illegible] years [illegible] years (New York)	Current smokers had more severe periodontal destruction (less dental [illegible] parameters) Mean LPA (mm) 0.496 Mean bone distance (height [illegible]	None
Mullally and Linden 1996	100 periodontal patients 50 current smokers (mean age 44 years) and 50 never smokers (mean age 46 years) Northern Ireland	Persons (%) with furcation involvement of ≥1 molar Current smokers 74 Never smoked 40 Molars with furcation involvement (%) Current smokers 39 Never smoked 16	Maxillary and mandibular 1st and 2nd molars were assessed radiographically; furcation involvement was defined as the area of radiolucency at furcation of the roots of at least 1 molar; molars with fused roots were excluded from the analysis
Alpagot et al. 1996	71 female and 46 male dental patients Aged 18–78 years United States (Minnesota)	Pearson correlation coefficients, pack-years Mean LPA (mm) 0.28 Mean PPD (mm) 0.27	An association between pack-years of smoking and the mean LPA or mean PPD was statistically significant in stepwise multiple linear regression models that also included age, enzyme levels in gingival crevicular fluid (β-glucuronidase, neutrophil elastase, myeloperoxidase), and plaque bacteria levels (*Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis, Eikenella corrodens,* and *Actinobacillus actinomycetemcomitans*)

[a]LPA = Loss of periodontal attachment.
[1]PPD = Probing pocket depth.
[2]CPITN = Community Periodontal Index of Treatment Needs.
[b]HIV = Human immunodeficiency virus.
[c]AZT = Azidothymidine or zidovudine, a medication used to treat HIV infections.

Table 6.22 Continued

Study	Population	Findings	Comments
Bridges et al. 1996	118 men with diabetes (46 with type I, 72 with type II) and 115 age-matched men without diabetes, from outpatient clinics Aged 24–78 years United States (Kentucky)	Pearson correlation coefficients for smoking and periodontal parameters Mean PPD[1] (mm) Diabetic 0.23 Nondiabetic 0.25 Mean LPA[a] (mm) Diabetic 0.34 Nondiabetic NR[3]	The mean PPD and LPA were described as higher among smokers with diabetes than among other groups, but the data were not reported. smoking was reported to be significantly associated with the mean PPD and LPA in a multiple linear regression model, but regression parameters were not reported; smoking included cigarettes, and pipes; the prevalence of tobacco use was not reported

[a]LPA = Loss of periodontal attachment.
[1]PPD = Probing pocket depth.
[3]NR = Data were not reported.

Table 6.22 Continued

Study	Population	Findings	Comments
Dolan et al. 1997a	Population-based sample of 471 adults Aged ≥35 years United States (Florida)	Prevalence (%) of teeth (≥1) with ≥7 mm LPA[a] Current smokers 49 Former smokers 33 Never smoked 37 OR (95% CI) for teeth (≥1) with ≥7 mm LPA Current smokers 1.9 (1.2–2.9) Former smokers 1.1 (0.8–1.6) Never smoked (referent) Teeth/person with 4–6 mm LPA (mean %) Current smokers 42 Former smokers 36 Never smoked 35 Teeth/person with ≥7 mm LPA (mean %) Current smokers 21 Former smokers 10 Never smoked 8	Estimates of prevalence and extent of LPA were significantly higher among current smokers but were not adjusted for other factors. OR estimates were adjusted for diabetes status, use of dental care services, tooth-brushing, flossing, and use of toothpicks
Hiroshima et al. 1997	Consecutive sample of 561 periodontal patients Aged 41–70 years United States (Missouri)	Correlation between pack-years and LPA (p < 0.05) Factors influencing LPA in a stepwise linear regression model: Smoking 0.61 Age[***] 0.57 Years since quitting 0.52 Years of smoking 0.47 Packs/day of cigarettes 0.04	smoking was the most significant factor associated with the mean LPA among current smokers

[a]LPA = Loss of periodontal attachment.
[***]Age was retained in the model because of its interaction with current smokers

Table 6.22 Continued

Study	Population	Findings	Comments
Imaki et al. 1997	1,611 male factory workers Aged 28–59 years Japan	Persons (%) with PPD[1] ≥4 mm by plaque bacteria levels, age, smoking status, and cigarettes/day Low plaque levels Aged 20–39 years Current smokers 16.1 1–20 14.3 ≥21 16.9 Former smokers 12.8 Never smoked 17.4 Aged 40–59 years Current smokers 43.7 1–20 40.5 ≥21 47.3 Former smokers 31.6 Never smoked 32.0 High plaque levels Aged 20–39 years Current smokers 49.7 1–20 49.3 ≥21 50.5 Former smokers 43.4 Never smoked 29.3 Aged 40–59 years Current smokers 84.8 1–20 81.3 ≥21 88.6 Former smokers 82.5 Never smoked 72.3	Used the CPITN[2] periodontal pocketing was significantly more prevalent among smokers than nonsmokers, and among persons with high plaque levels
Tezal 1997	Consecutive sample of 368 dental patients Aged 20–83 years Japan	Prevalence (%) of PPD ≥4 mm Ever smoke, smoke now, yes Aged 20–29 years Smokers [illegible] Nonsmokers [illegible] Aged 30–39 years Smokers 21.7 Nonsmokers 16.8 Aged 40–49 years Smokers [illegible] Nonsmokers 27.7	Data included [illegible] periodontal [illegible] [illegible] [illegible]

Table 6.22 Continued

Study	Population	Findings	Comments
Axelsson et al. 1998	Population-based sample of 536 men and 557 women Aged 35, 50, 65, and 75 years Sweden	Mean number of missing teeth Aged 35 years Smokers 2.0 Nonsmokers 1.6 Aged 50 years Smokers 6.3 Nonsmokers 4.8 Aged 65 years Smokers 13.8 Nonsmokers 10.3 Aged 75 years Smokers 18.8 Nonsmokers 13.0 Molars with furcation involvement (mean %) Aged 35 years Smokers 6.3 Nonsmokers 2.7 Aged 50 years Smokers 28.3 Nonsmokers 14.5 Aged 65 years Smokers 42.0 Nonsmokers 22.5 Aged 75 years Smokers 60.0 Nonsmokers 33.5 Mean LPA (mm) Aged 35 years Smokers 1.1 Nonsmokers 0.7 Aged 50 years Smokers 2.4 Nonsmokers 1.5 Aged 65 years Smokers 3.1 Nonsmokers 2.3 Aged 75 years Smokers 4.0 Nonsmokers 2.7	Former smokers were excluded from the analysis; the mean number of missing teeth was significantly higher among smokers for all ages except 35 years; the mean percent of molars with furcation involvement was higher for all age groups except 75 years; the LPA* was measured at mesial surfaces of all teeth

*LPA = Loss of periodontal attachment.

Table 6.22 Continued

Study	Population	Findings	Comments
Gunsolley et al. 1998	Dental patients 142 nonsmokers and 51 smokers without periodontitis Mean age = 30.9 years United States (Virginia)	Mean LPA* (mm) Smokers 0.28 Nonsmokers 0.17 Teeth with ≥1 LPA site ≥2 mm (mean %) Smokers 17.0 Nonsmokers 9.9 Teeth with ≥1 LPA ≥5 mm (mean %) Smokers 1.5 Nonsmokers 0.4	Analysis of covariance; covariates included age, race, gender, and mean plaque index score
[illegible]	Population-based sample of 2[illegible] women and 1[illegible] men Aged 20–70 years Sweden	[illegible]	[illegible]
Persson et al. 1998	40 dental patients Ages 35–54 years United States All smokers	Smokers were more likely than nonsmokers to have ≥1 periodontal pocket ≥4 mm and ≥1 site with ≥3 mm loss of attachment	[illegible]
Shimazaki et al. 1998	352 male and 58 female factory workers Ages 20–59 years Japan	OR (95% CI) for association of deep gingival pockets Current smoker 2.1 (1.2, 3.8)	Multivariate analysis of CPITN* was adjusted for [illegible]

*LPA = Loss of periodontal attachment.
*CPITN = Community Periodontal Index of Treatment Needs.
†ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Xanma et al. 1999	40 male and 20 female dental patients with early onset periodontitis Aged 22–35 years Greece	Mean number (%) of periodontal sites with PPD* ≥ 5 mm Smokers 76.3 (54.1) Nonsmokers 57.5 (39.6) Mean PPD (mm) per diseased site Smokers 6.9 Nonsmokers 5.9 Mean LPA* (mm) per diseased site Smokers 7.6 Nonsmokers 6.5	There was no control group
[illegible] et al. 1999	[illegible] male and [illegible] female periodontal patients Aged <35 years (mean age = 28 years; minimum age not specified) Northern Ireland	Alveolar bone loss (mean %) Current smokers 31.7 Never smoked [illegible]	The only criteria for periodontitis was [illegible] with ≥20% radiographic bone loss, aged <35 years, with no medical condition or drug therapy known to affect periodontium; smoking was not significantly associated with the mean percent of bone loss in this ANOVA† model that included age and disease status (generalized vs. localized); there was no control group

*LPA = Loss of periodontal attachment.
*PPD = Probing pocket depth.
†ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Wakai et al. 1999	517 male and 113 female participants in a multiphasic health examination Aged 23–83 years Japan	Adjusted OR (95% CI) for "periodontal disease" by smoking status Current smokers (cigarettes/day) 0–19 2.3 (1.2, 4.3) 20–39 [illegible] ≥40 [illegible] Former smokers [illegible] Never smoked [illegible]	This ordinal logistic regression model with CPITN* scores as outcomes was adjusted for age, gender, fasting plasma glucose, and dental debris index; a dose-response relationship was highly significant
Kardaris, Bondemark, and Wikesjö 2000	93 male and 23 female dental patients in the [illegible] 60 never smokers) Aged 20–40 years Greece	Mean PPD (mm) by smoking status Current smokers [illegible] Never smoked [illegible] Mean LPA* (mm) by smoking status Current smokers [illegible] Never smoked [illegible] Percent ≥4 mm attachment loss Current smokers [illegible] Never smoked [illegible] Percent with LPA ≥4 mm by smoking status Current smokers [illegible] Never smoked [illegible]	Multivariate analysis of [illegible]
Mora Arca et al. 2000	304 male military recruits Mean age 19 years Spain	Mean PPD (mm) by smoking status Current smokers 1.68 Nonsmokers 1.58 Mean LPA (mm) by smoking status and cigarettes/day Current smokers 1.82 <5 1.83 5–20 1.82 >20 1.79 Nonsmokers 1.63	It is unclear if [illegible] nonsmokers included former smokers

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
*CPITN = Community Periodontal Index of Treatment Needs.

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Table 6.22 Continued

Study	Population	Findings	Comments
Tomar and Asma 2000	Population-based sample of 6,460 men and 7,160 women Aged ≥18 years United States	Adjusted OR for periodontitis and smoking Current smokers (all) 4.0 (3.2–4.9) Cigarettes/day ≤9 2.8 (1.9–4.1) 10–19 3.6 (2.7–4.8) 20 4.7 (3.5–6.4) 21–30 5.7 (3.9–8.2) 7.5) ≥31 5.9 (4.0–8.6) 8.6) Former smokers (all) 1.7 (1.3–2.2) Years since quitting 0–2 3.2 (2.2–4.6) 3–5 2.2 (1.5–3.4) 6–10 2.0 (1.4–3.0) ≥11 1.2 (0.9–1.6) Never smoked 1.0 (referent)	Periodontitis was defined as 1 or more periodontal sites with both PPD[a] ≥4 mm and LPA[b] ≥4 mm; there were strong dose-response relationships for current smokers (cigarettes/day and duration) and former smokers (years since quitting)

[a]LPA = Loss of periodontal attachment
[b]PPD = Probing pocket depth

Table 6.23 Cohort studies on the association between smoking and periodontitis

Study	Population	Follow-up (years)	Outcome	Findings
Bolin et al. 1986	170 men and 179 women Aged 18–65 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of root length) by baseline smoking status and cigarettes smoked/day, standardized for plaque level Current 1–9 cigarettes/day 5.1 10–20 cigarettes/day 5.5 >20 cigarettes/day 5.6 Nonsmokers 4.9 Unclear if nonsmoker or quit/former smoker
Beck et al. 1987	65 [illegible] the Veterans Administration Normative Aging Study, Univ. of Rochester	8	[illegible] mean [illegible] with smoking and radiographic alveolar bone loss	Mean change in PPD by baseline smoking status Smokers 0.162 Nonsmokers 0.059 Mean change in attachment loss Smokers 0.260 Nonsmokers 0.202 Mean change in alveolar bone level Smokers 0.257 Nonsmokers 0.172
Ismail et al. 1990	101 persons Aged 18–68 years at baseline United States (Detroit)	15	Change in [illegible]	OR[c] = 14.2 (95% CI[d] 3.1–62.2) for smokers (≥1 cigarette/day vs. 0); this multiple logistic regression model also included years of [illegible] and [illegible]
Bolin et al. 1992	121 men and 170 women Aged 35–55 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of root length) [illegible] by baseline smoking status and cigarettes smoked/day Smokers 5.7 1–9 cigarettes/day 5.2 10–20 cigarettes/day 6.0 >20 cigarettes/day 6.3 Ever 5.4 [illegible] 4.9 Never 4.4

[c]OR = Smoking prevalence ratio, estimated by odds ratio
[d]LPA = Loss of periodontal attachment.
[e]OR = Odds ratio.
[f]CI = Confidence Interval.

Table 6.23 Continued

Study	Population	Follow-up (years)	Outcome	Findings
Brown et al. 1994	611 community-dwelling persons Aged ≥65 years at baseline United States (North Carolina)	1.5	2 or more sites with incident LPA[a] ≥3 mm	OR = 3.4 (95% CI, 1.6–7.5) among white adults who smoked cigarettes regularly; this logistic regression model included levels of *Porphyromonas gi* most recent of d
Machtei et al. 1999	258 [illegible] periodontal patients Aged 18–75 years at baseline United States (Texas)	3	Attachment and bone loss	[illegible] for [illegible] progression
Beck et al. 1997	547 persons Aged ≥65 years at baseline United States (North Carolina)	5	At least 1 periodontal site with LPA ≥3 mm	RR[b] = [illegible] of smokers with level of the periodontal site [illegible] group included both [illegible] former smokers; this logistic regression [illegible] so included *Porphyromonas g* [illegible] status, number of missing teeth, tooth type, periodontal site type, educational attainment, and [illegible]
Machtei et al. 1999	445 [illegible] adults with moderate periodontitis Ages 35–65 years at baseline Upper State New York	3	Increased periodontal probing or bone loss exceeding 2 standard deviations based on baseline [illegible]	OR = 3.41 (95% CI, [illegible]) for smokers as compared with [illegible] Sites that experienced ≥[illegible] of attachment loss: Smokers 8.3% Nonsmokers 4.5% Mean periodontal attachment loss (mm): Smokers 0.27 Nonsmokers 0.09 Mean bone height loss (mm): Smokers 0.23 Nonsmokers 0.12 Sites with bone height loss (mm): Smokers 15.1 Nonsmokers 7.4

[a]LPA = Loss of [illegible] attachment
[b]RR = Relative risk.

Table 6.23 Continued

Study	Population	Follow-up (years)	Outcome	Findings
Etter et al. 1999	697 community-dwelling persons Aged ≥65 years at baseline United States (North Carol [illegible])	7	At least 1 site with incident LPA[a] ≥3 mm	RR = 1.4 (95% CI, 1.1–1.7) among whites and 1.5 (95% CI, 1.0–2.2) among blacks for current smoking; multivariate Poisson regression models included a number of site-level and person-level variables
Machtei et al. 1999	21 [illegible] with moderate periodontitis Aged 25–75 years at baseline United States (New York)	2.5	Mean annual LPA	Mean annual LPA (mm): Smokers [illegible] 22 nonsmokers 0.10 Sites experiencing ≥2 LPA (mm): Smokers 9.6% Nonsmokers 4.3% Smoking was a strong predictor of annual changes in PPD[b] in a multiple linear regression analysis
Nordenram et al. 1999	Population-based sample of 67 persons Age 70, 80, and 90 years at baseline Sweden	12	[illegible] in the [illegible] after [illegible]	The [illegible] smoking and [illegible]
Bain et al. 2001	456 [illegible] adult inserters Aged 18–55 years Australia	3	[illegible] sites with PPD ≥5 mm	[illegible] Smokers had 2.9 [illegible] [illegible] [illegible]

Table 6.24 Cross-sectional and cohort studies on the association between smoking and dental caries

Study	Population	Design	Results
Ludwick and Massler 1952	2,577 male navy enlistees Aged 17–21 years United States	Cross-sectional	Mean DMFS[a] by mean number of cigarettes/day Cigarettes/day — DMFT[b] — DMFS 0 — 9.5 — 20.4 5 — 9.1 — 20.5 10 — 9.8 — [illegible] 15 — 9.75 — 21.2 ≥20 — [illegible] — 23.0 A statistically significant difference was reported for DMFT and DMFS scores between those smoking 5 cigarettes/day and those smoking 15 cigarettes/day
Amler and Dell 1960	1,851 male recruits Aged 18–20 years Indiana	Cross-sectional	Mean DS and DMFS by cigarettes/day Cigarettes/day — DS — DMFS 0 — 13.8 — 36.4 1–9 — 20.7 — 51.7 10–20 — 19.9 — 49.5 >20 — 23.3 — 58.5 Trend — p<0.05 — p<0.01
Mejàre et al. 1988	21 monozygotic twin pairs Aged 13–14 years Sweden	Cross-sectional	The twin with more cigarettes/day had a significantly higher mean DMFS than the twin who smoked less and filled surfaces ($t = 2.65$, $p < 0.05$). In this subgroup, χ^2 for DMFS = 3.29
Zitterman et al. 1990	Private dental patients Aged 18–64 years 184 current smokers 301 former smokers [illegible] never smokers United States [illegible]	Cross-sectional	Mean DS — DMFS Current smokers — 5.3 — 14.9 Former smokers — 7.4 — 19.1 Never smoked — [illegible] smokers — [illegible]

[a]DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
[b]DMFT = Decayed, missing (due to caries), or filled permanent teeth.
[c]DS = Decayed coronal permanent tooth surfaces.
[d]PV = Prediction values.
[e]MS = Missing tooth surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Hirsch et al. 1991	1,122 male and 1,023 female dental patients Aged 14–19 years Sweden	Cross-sectional	Mean DMFT[b] by smoking status (but not adjusted for age) Smokers — 9.0 Nonsmokers — 7.0 The test suggests that smoking was significantly associated with DMFT across age groups, but data were not presented
Krall et al. 1991	[illegible] persons ≥20 to 74 years and 787 persons aged 75 years Sweden	Cross-sectional	Among persons aged 75 years, smokers had more DFS[c] than nonsmokers ($p < 0.05$, Student's t-test comparing means)
Locker 1992	Population-based sample 907 persons Aged ≥50 years Canada (Ontario)	Cross-sectional	Mean DFS[d], DMFS[e], and RDS[f] by smoking status DFS — DMFS — RDS Current smokers — 1.2 — 6.1 — 1.2 Former smokers — 0.8 — 4.7 — 0.8 Never smoked — 0.7 — 4.2 — 0.6
Kyle et al. 1992[g]	[illegible] case-control [illegible] years old [illegible]	Case-control	Odds ratios were significantly higher than never smokers to have current for medical conditions, [illegible] and medications, but were not significant
Kendell et al. 1993	[illegible] years	Cohort, [illegible] follow-up	Estimated 3-[illegible] smoking cessation [illegible] and mean [illegible] among [illegible] smoking [illegible]
Beiswanger et al. 1994	[illegible] case-control [illegible]	Cross-sectional	Mean decayed teeth was not stratified by smoking status Smokers — 15.5 Nonsmokers — 13.0
Hart et al. 1995	Convenience sample 200 dental patients Aged 14–88 years United States (Tenne[illegible]	Cross-sectional	No significant difference in mean DMFT between smokers (23.9) and nonsmokers (21.2), not age-adjusted; unclear if missing teeth included only those missing due to dental caries

[b]DMFT = Decayed, missing (due to caries), or filled permanent teeth.
[c]DS = Decayed coronal permanent tooth surfaces.
[d]DFS = Decayed or filled coronal permanent tooth surfaces.
[e]FS = Filled coronal permanent tooth surfaces.
[f]RDS = Decayed root surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Locker 1995	Population-based sample 498 persons (of 699 in the baseline survey) Aged ≥50 years at baseline Canada (Ontario)	Cohort, 3-year follow-up	Mean RDFS[a] and RDS[b] increments by smoking status RDFS — RDS Current or former smokers — 0.75 — 0.36 Never smoked — 0.47 — 0.24 Persons (%) experiencing RDFS or RDS increments (≥1) by smoking status (RDS differences were not statistically significant) RDFS — RDS Current or former smokers — 31.6 — 19.0 Never smoked — 24.0 — 12.7 Smoking was not a significant predictor of RDFS or RDS increments in this multiple logistic model
Fiske et al. 1995	Nonrandom convenience population-based sample 344 blacks, 219 whites Aged ≥65 years United States [illegible]	Cohort, 3-year follow-up	RDFS level [illegible] years [illegible] increments [illegible] $n = 25$ [illegible] in this [illegible] were not significant
Axelsson et al. 1996	Population-based sample Aged 35 y[illegible] (n = 1,5) Aged 50 y[illegible] (n = 3[illegible]) Aged 65 y[illegible] (n = 410) Aged 75 y[illegible] (n = 310) Sweden	Cross-sectional	Mean DFS[c] by age and smoking status Aged 35 years Current smokers — 48.9 Never smoked — 38.1 Aged 50 years Current smokers — 84.4 Never smoked — 76.7 Aged 65 years Current smokers — 98.8 (not significant) Never smoked — 89.0 Aged 75 years Current smokers — 114.6 Never smoked — 100.2 Largest difference at ages 50, 65, and 75 years was in the number of MS[d] at 35 years, smokers had a higher mean DFS than never smokers (38.5 vs. 31.2); MS were not limited to those missing teeth due to caries

[a]DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
[b]MS = Missing tooth surfaces.
[c]DFS = Decayed or filled coronal permanent tooth surfaces.
[d]RDS = Decayed root surfaces.
[e]RDFS = Decayed or filled root surfaces.

Table 6.24 Continued

Study	Population	Design	Results
Tomar and Winn 1999	Population-based sample 6,845 dentate men Aged ≥18 years United States	Cross-sectional	Mean DFT[a], DFS[b], and RDFS[c] by smoking status, adjusted for age, race, and ethnicity DFT — DFS — RDFS Current smokers — 9.3 — 16.0 — 2.3 Never smoked — 7.0 — 17.4 — 1.1 DFT and DFS differences were not statistically significant; current smokers were not significantly more likely than men who had never used tobacco to have ≥1 RDFS in multiple logistic regression models

[a]DFS = Decayed or filled coronal permanent tooth surfaces.
[b]RDFS = Decayed or filled root surfaces.
[c]DFT = Decayed or filled permanent teeth.

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Erectile Dysfunction

Erectile dysfunction, defined as the persistent inability to attain and maintain penile erection adequate for satisfactory sexual performance (National Institutes of Health [NIH] Consensus Development Panel on Impotence 1993), has recently received considerable attention as a major medical issue in the United States. Additional emphasis has been given to this condition with increasing recognition of its profound impact on quality of life (Wagner et al. 2000). Epidemiologic data, though sparse, indicate its importance as a public health problem. The prevalence of erectile dysfunction in 1992 was estimated to be 18 percent among men 59 through 59 years of age according to the National Health and Social Life Survey, a United States probability sample of men and women aged 18 through 59 years (Laumann et al. 1999). Among men 40 through 70 years of age, prevalence estimates of complete erectile dysfunction during 1987–1989 exceeded 10 percent and estimates of at least mild erectile dysfunction exceeded 50 percent, according to the Massachusetts Male Aging Study (Feldman et al. 1994). Incidence estimates of erectile dysfunction during 1995–1997, derived from longitudinal results of the Massachusetts Male Aging Study, approach 26 cases per 1,000 men annually (Johannes et al. 2000).

Many conditions have been implicated as causes of erectile dysfunction, including hormonal derangement, psychogenic influences, neurologic disorders, and vascular impairment, which may all interfere with the basic physiologic mechanisms involved in penile erection. Vascular impairment, which commonly refers to disease states that hamper penile blood flow, warrants particular attention for several reasons. Most importantly, vascular diseases are commonly associated with presentations of erectile dysfunction. Objectively demonstrable erectile dysfunction has been found in patients with myocardial infarction, coronary bypass surgery, cerebral vascular accidents, peripheral vascular disease, and hypertension (Melman and Gingell 1999). Furthermore, reports of patients with vasculogenic erectile dysfunction have suggested predisposing vasculopathic risk factors, which include cigarette smoking, fatty diets, adverse serum lipid levels, hypertension, physical inactivity, and obesity (Goldstein and Hatzichristou 1994). Several large epidemiologic studies have explored the extent to which these factors impair erectile function (Feldman et al. 1994; Derby et al. 2000b; Feldman et al. 2000; Johannes et al. 2000). The results of these studies also imply that modifications of risk factors may reduce the occurrence of erectile dysfunction.

Among widespread concerns about adverse health effects associated with cigarette smoking is the growing belief that this activity adversely affects sexual health and, in particular, erectile function. It is plausible that cigarette smoking exerts atherogenic effects on penile circulation relevant to erectile function, akin to effects on coronary circulation associated with heart disease (Fried et al. 1986; Raitchen et al. 1988). Furthermore, cigarette smoking cessation may afford a preventive strategy for reducing erectile dysfunction rates. However, each of these hypotheses requires a critical examination of the evidence regarding the effects of smoking on penile erection. This chapter summarizes and evaluates current observational and experimental data linking cigarette smoking and tobacco use with erectile dysfunction, including the pathophysiologic concepts.

Conclusions of Previous Surgeon General's Reports

This topic has received some coverage in prior Surgeon General's reports. The 1984 report (U.S. Department of Health, Education, and Welfare [USDHEW] 1984) included a discussion on masculinity in relation to COPD. The discussion drew from an investigation that defined the "element of masculinity as indicated by external morphologic features," and contended that "weakness of the masculine component is significantly more frequent in smokers than in nonsmokers, and most frequent in heavier smokers" (USDHEW 1984, pp. 383–4). This vaguely described element merely relates to the theme of male sexual prowess, as erectile ability or lack thereof was not directly assessed. The Advisory Committee to the Surgeon General recognized the tentative nature of the conclusions and the need for further confirmation. The 1990 report carried out a comprehensive review of sexual activity and performance, and sperm density and quality (USDHHS 1990). This review did not lead to specific conclusions, reflecting limitations of the available data and their inconsistency. This section reviews the issue of male sexual function, examining the influence of cigarette smoking on penile erection, one specific component of male sexual function.

Biologic Basis

Direct biologic evidence establishing plausible mechanisms for the effects of cigarette smoking on penile erection certainly would strengthen the premise that cigarette smoking constitutes a risk factor for erectile dysfunction. One possible mechanism is smoking-induced endothelial dysfunction of the penile vasculature. This hypothesis is supported by recent investigations into the physiology of penile erection affirming that the endothelium of the blood vessels supplying the penis, as well as that lining the lacunar spaces within the penis, releases vasoactive substances that contribute to the control of penile smooth muscle relaxation required for penile erection (Lue and Taneghe 1987).

Saenz de Tejada and colleagues (1989) probed whether smoking affects penile vasculature endothelium as part of an investigation of the consequences of diabetes mellitus on endothelial function in the penis in men with erectile dysfunction. Using isolated strips of human corpora cavernosa of the penis, the investigators compared isometric tension results from men with and without diabetes who were smokers (having at least a five pack-year history of cigarette smoking) or nonsmokers. The findings indicate that a history of smoking was not associated with a worsened impairment of endothelium-mediated relaxation responses. The study did not assess responses of tissue from smokers independently while controlling for other possible erectile dysfunction risk factors, nor did it carry out a subset analysis of responses from smokers specified to have had large amounts of cigarette smoke exposure. These limitations restrict the conclusions that can be drawn concerning the effects of smoking on endothelial function in the penis.

In a study of rats, Xie and colleagues (1997) examined the long-term effects of smoking on the endothelial synthesis of nitric oxide in the penis. Nitric oxide is now known to be the principal vasoactive mediator of penile erection (Burnett 1997). Nitric oxide is released by endothelial cells in response to direct cholinergic stimulation and in response to dynamic factors of changing penile blood flow. In the study, rats were passively exposed to cigarette smoke in 60-minute sessions once per day, five days per week, for eight weeks. Immunoblot analyses of the protein expression of endothelial nitric oxide synthase (eNOS) in penile tissue from the exposed rats did not reveal any diminution of eNOS expression compared with tissue from control rats. However, these investigators confirmed that overall nitric oxide synthase enzymatic activity (which combines neuronal and endothelial sources) and specifically the protein expression of the neuronal form of nitric oxide synthase in the penis were both markedly reduced following passive exposure to cigarette smoke in rats as compared with rats not exposed to smoke. Their findings mainly suggest that smoking selectively impairs neuronal mechanisms. In particular the neurorally based nitric oxide signal transduction pathway associated with penile erection. But the relevance of the rat model for humans is uncertain.

The investigation by Saenz de Tejada and colleagues (1989) also evaluated whether smoking affects the neurogenic mechanisms responsible for penile erection. The overall finding was that the impairment of neurogenically mediated relaxation of penile smooth muscle from smokers (combining results from men with and without diabetes) was not different from the impairment observed in nonsmokers (both men with and without diabetes). However, these conclusions have the same limitations as those concerning endothelial effects observed in this study (see above). An in vitro investigation of neuromuscular transmission in human corpus cavernosum also studied nicotine and found that the actions of this agent are both contractile and relaxant (Adaikan and Ratnam 1988). If erectile dysfunction results from exogenously administered nicotine during cigarette smoking, it may be due to the acute vasoactive modulatory effects of this agent on the penile vasculature.

Epidemiologic Evidence

Observational Data

This section explores the association between cigarette smoking, as well as other forms of tobacco use, and the occurrence of erectile dysfunction based on a review of available observational data. A literature search was conducted using the National Library of Medicine's PubMed system and was supplemented with professional knowledge of other resources. The critical feature of the observational data is the necessary reliance on self-reporting and other subjective instruments (e.g., logs, questionnaires, and sexual function inventories) to determine tobacco exposure and erectile performance, rather than quantitative measurements of these variables. A single-item assessment (e.g., "Do you experience difficulty getting and/or maintaining an erection that is rigid enough for satisfactory sexual intercourse?") has gained prominence particularly for population-based epidemiologic studies (Derby et al. 2000a). This assessment has been

useful as a single, direct practical tool to ascertain the presence of erectile dysfunction, whereas clinical questions are impractical (Derby et al. 2000a). This data collection methodology does introduce the possibility of information bias, probably toward underreporting. Differential underreporting by smoking status would bias estimates of the effects of smoking; however, the findings do prove insightful as to its probable significance within the general population. Furthermore, aspects of compromised sexual function are fundamentally issues of a subjective nature, wherein patient self-reporting may accurately serve as the main, or even the sole, criterion for establishing the existence and severity of the problem.

Case Series

Cigarette smoking has been linked to erectile dysfunction in several clinical reports, most qualifying as observational case series. As such, they are limited by not having true comparison groups, but they are reviewed here because they are often cited and data from more formal studies are limited. Wabrek and colleagues (1983) found that approximately 50 percent of 120 men referred for evaluation and management of erectile dysfunction to a hospital-based medical sexology program were smokers, counting users of cigarettes, cigars, or pipes. Virag and colleagues (1985) confirmed a 64 percent rate of cigarette smoking, defined as tobacco use exceeding 15 cigarettes per day for at least 15 years, among 440 men referred for clinical evaluation of erectile dysfunction. Bortman and Du Plessis (1988) similarly observed a 62 percent cigarette smoking rate, based on approximately 25 cigarettes per day for more than 20 years among 300 men screened at an andrology clinic. An attempt to provide comparative information was made by Condra and colleagues (1988), who studied 178 men with erectile dysfunction referred for clinical evaluation and found that 51.4 percent were current smokers and 81 percent were current or former cigarette smokers. These rates exceeded the 38.6 percent and 58.3 percent rates, respectively, ascertained in the general population using concurrent survey data. A recently published meta-analysis of smoking prevalence in men with erectile dysfunction also included a comparative assessment that controlled for age distribution, time period, and geographic location (Tengs and Osgood 2001). This meta-analysis, which consisted of 10 clinical studies published in the last 20 years with data on current smoking, revealed that 40 percent of the combined total of 3,819 men with erectile dysfunction were current smokers compared with 20 percent of men in the general population (Tengs and Osgood 2001).

Population-Based Studies

More valid appraisals of the effects of cigarette smoking on erectile dysfunction have been obtained through cross-sectional, random surveys of a sample population (Table 6.25). The Vietnam Experience Study of 1985–1986, which surveyed 4,462 U.S. Army Vietnam-era veterans aged 31 through 49 years, found erectile dysfunction prevalence rates of 2.2 percent among nonsmokers, 2.0 percent among former smokers, and 3.7 percent among current smokers ($p = 0.005$). The association (OR = 1.5 [95 percent CI, 1.0–2.2]) was maintained even after adjustments for comorbidity factors including vascular disease, psychiatric problems, hormonal factors, substance abuse, marital status, race, and age (Mannino et al. 1994).

Additional recent studies support the direct association between cigarette smoking and erectile dysfunction. A cross-sectional study assessing the prevalence of erectile dysfunction in 2,010 men aged over 18 years in Italy in 1998–1987 showed that smoking was associated with an increased risk of the condition (Parazzini et al. 2000). Although the study was controlled for multiple variables including age, marital status, SES, and chronic diseases, it found an increased risk of erectile dysfunction for current smokers (OR = 1.7 [95 percent CI, 1.2–2.4], $p < 0.05$) and for former smokers (OR = 1.6 [95 percent CI, 1.1–2.3], $p < 0.05$) in comparison with lifetime nonsmokers (Parazzini et al. 2000). The Krimpen Study, a community-based study conducted in Rotterdam, the Netherlands, between 1995 and 1999 that surveyed 1,688 men aged 55 to 78 years, also confirmed that smokers professed significant erectile dysfunction (adjusted OR = 1.6 [95 percent CI, 1.1–2.3], $p < 0.05$) to a greater extent than nonsmokers (Blanker et al. 2001). A cross-sectional study of erectile dysfunction prevalence conducted in Spain in 1998–1999, consisting of 2,476 men aged 25 to 75 years, demonstrated that cigarette smoking was significantly associated with erectile dysfunction (adjusted OR = 2.5 [95 percent CI, 1.64–3.80], $p < 0.05$) (Martin-Morales et al. 2001).

Another recent study supports the direct association between cigarette smoking and erectile dysfunction (Bacon et al. 2001). The Health Professionals Follow-up Study, a prospective cohort study of heart disease and cancer among U.S. male health professionals (Rimm et al. 1991; Ascherio et al. 1996), surveyed 34,282 men aged 53 through 90 years in 2000. The study showed an increased probability of erectile dysfunction among current smokers compared with nonsmokers (OR = 1.3 [95 percent CI, 1.1–1.6], $p < 0.05$), while controlling for age, marital status, and chronic diseases (Bacon et al. 2001).

Table 6.25 Cross-sectional studies on the association between smoking and the risk of erectile dysfunction (ED)

Study	Population	Smoking status	ED rate (%)	p value
Feldman et al. 1994[a]	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1989	Never and former smokers Current smokers	9.3 11.0	>0.200
Mannino et al. 1994[a]	U.S. veterans aged 31–49 years; studied during 1985–1986	Never smokers Current smokers Former smokers	2.2 3.7 2.1	0.005[b]
Feldman et al. 2000[c]	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1989	Never and former smokers Current smokers	14 24	0.010
Parazzini et al. 2000[a]	Italian men aged ≥18 years; studied during 1998–1987	Never smokers Current smokers Former smokers	24.2 35.6 40.2	NR[d]
Bacon et al. 2001[a]	U.S. male health professionals aged 53–90 years; studied in 2000	Never smokers Current smokers Former smokers	27.4 ? 26.6	NR
Blanker et al. 2001[a]	Dutch men aged 55–78 years; studied during 1995–1999	Never and former smokers Current smokers	NR NR	NR
Martin-Morales et al. 2001[a]	Spanish men aged 25–95 years; studied during 1998–1999	Never and former smokers Current smokers	NR NR	NR

[a]Prevalence study.
[b]Significant results.
[c]Incidence study.
[d]NR = Data were not reported.

Evidence against an independent association between cigarette smoking and erectile dysfunction comes from the baseline phase of the Massachusetts Male Aging Study, a community-based survey conducted from 1987–1989 of 1,290 men aged 40 through 70 years living in the Boston, Massachusetts, area (Feldman et al. 1994). The probabilities of complete erectile dysfunction were 11 percent in smokers and 9.3 percent in nonsmokers, including both former smokers and those who had never smoked ($p > 0.20$) (Feldman et al. 1994). However, the longitudinal phase of the Massachusetts Male Aging Study, extending over a nine-year median interval, showed the comorbidity-adjusted rate of incident erectile dysfunction to be significantly higher among cigarette smokers (24 percent) than nonsmokers (14 percent) (OR = 1.97 [95 percent CI, 1.07–3.63], $p = 0.03$) (Feldman et al. 2000). The classification of erectile dysfunction was based on an algorithm derived by the discriminant analysis of 13 questions.

Kleinman and colleagues (2000) reanalyzed the baseline data from the Massachusetts study using new methods for classifying erectile dysfunction. One method corresponded to the approach used by Feldman and colleagues (2000), based on responses from men attending a urology clinic to an original

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questionnaire and to an additional global question for self-rating erectile dysfunction. Another analysis was based on responses to an expanded follow-up questionnaire. Cross-sectional analyses of predictors of erectile dysfunction were carried out in the 1987–1989 baseline data. With the clinic-based method for classification, current smoking was not associated with erectile dysfunction (OR = 0.95 [95 percent CI, 0.72–1.22]) while with the study-based method it was (OR = 1.39 [95 percent CI, 1.07–1.80]).

Disease Correlates

Type of Tobacco Exposure. The prospective analysis of the Massachusetts Male Aging Study examined various types of tobacco exposures to identify associations with erectile dysfunction. The odds of incident erectile dysfunction were more than doubled both for passive exposure to cigarette smoke, if present both at home and at work (adjusted OR = 2.07 [95 percent CI, 1.04–4.13]) ($p = 0.04$), and for cigar smoking (adjusted OR = 2.45 [95 percent CI, 1.09–5.50]) ($p = 0.03$). Passive exposure at home or at work alone did not increase the odds of incident erectile dysfunction in nonsmokers, but each increment of exposure did increase the estimated likelihood of erectile dysfunction in smokers (Feldman et al. 2000).

Dose-Response. The relationship between the amount of tobacco exposure and the extent of erectile dysfunction has been subjected preliminarily to epidemiologic analyses. Several population-based studies further explored the effects of measures of exposure on erectile dysfunction. The Vicoram Experience Study did not show any relationship between the number of cigarettes smoked daily or the number of years smoked and erectile dysfunction among currently smoking veterans (Mannino et al. 1994). Similarly, the baseline phase of the population-based Massachusetts Male Aging Study did not reveal any dependence of packs per day or lifetime pack-years smoked on reported erectile dysfunction among current smokers (Feldman et al. 1994). By contrast, an Italian cross-sectional study showed an increased erectile dysfunction risk with duration of the behavior, based on an OR of 1.6 (95 percent CI, 1.1–2.3) for men smoking 20 or more years and an OR of 1.2 (95 percent CI, 1.0–2.4) for men smoking less than 20 years (Parazzini et al. 2000).

Risk Factor Covariates and Effects of Medication. The combined effects (i.e., synergistic or additive interactions) of cigarette smoking and other risk factors in the development of erectile dysfunction have been analyzed. Goldstein and colleagues (1994) examined clinical characteristics in 19 patients who underwent pelvic irradiation for prostate cancer, finding that 14 out of 15 who displayed diminished erectile capacity were cigarette smokers, whereas only 1 out of 4 who preserved erectile capacity was a cigarette smoker. The strong association of cigarette smoking with erectile impairment in this study led the investigators to propose a synergistic role of smoking, and conceivably other vasculopathic risk factors, with the radiation effects associated with radiation-induced erectile dysfunction (Goldstein et al. 1994). In the baseline phase of the Massachusetts Male Aging Study, Feldman and colleagues (1994) found that cigarette smoking did not constitute an independent risk factor for erectile dysfunction; however, in that same study, the association of erectile dysfunction with certain risk factors was greatly amplified in current cigarette smokers. This amplification was demonstrated for persons having erectile dysfunction with treated heart disease (from 21 percent for current nonsmokers to 58 percent for current smokers), treated hypertension (from 8.5 to 28 percent), and untreated arthritis (from 9.4 to 20 percent), and for those persons receiving various medicalient including cardiac drugs (from 14 to 41 percent), antihypertensive medications (from 7.5 to 21 percent), and vasodilators (from 21 to 52 percent). Similarly, in an Italian cross-sectional study, smoking increased the adjusted ORs for erectile dysfunction associated with diabetes by 13 percent and with hypertension by 38 percent (Parazzini et al. 2000).

Effects of Smoking Cessation. The hypothesis that cigarette smoking adversely affects erectile function would seemingly be strengthened by epidemiologic evidence demonstrating that smoking cessation leads to erectile function recovery. Forsberg and colleagues (1979) presented the case reports of two cigarette smokers aged 26 and 27 years with erectile dysfunction whose erectile function returned in concordance with improved penile vascular testing results following smoking cessation. Elist and colleagues (1984) determined that 8 (40 percent) out of 20 men with erectile dysfunction who had smoked one to two packs of cigarettes per day for at least 15 years recovered functional erections after abstaining from cigarette smoking for six weeks. In this study, seven responders (35 percent) were confirmed by objective testing criteria to have recovered normal erectile activity from baseline abnormal levels.

Population-based reports add additional perspectives to the premise that modifying cigarette smoking behavior affects the occurrence of erectile dysfunction. One study in this regard is the Vietnam Experience Study of 1685–1886, which determined that the prevalence of erectile dysfunction among former smokers was comparable to that among nonsmokers, and the prevalence rates were significantly lower than those found in current smokers (Mannino et al. 1994). Similarly, the longitudinal phase of the Massachusetts Male Aging Study determined that incident erectile dysfunction was no more likely among former smokers than among nonsmokers, in contrast to current smokers (Feldman et al. 2000). Results from the Health Professionals Follow-up Study also suggest that former smokers carry a lower risk of erectile dysfunction than current smokers, although this risk for former smokers still exceeds that of nonsmokers (Bacon et al. 2001).

From these population-based study results, one might further conclude that the discontinuation of smoking results in a recovery of functional erection status. However, this simple conclusion is challenged by recent results from the prospective evaluation of men participating in the Massachusetts Male Aging Study who discontinued smoking during the almost nine-year follow-up period of this study. This latter analysis found that the covariate-adjusted incidence of erectile dysfunction was not significantly reduced after smoking discontinuation ($p = 0.28$). Important considerations of this investigation are that the men who quit smoking had begun smoking at an early age (mean age 16.6 years) and had accumulated a high lifetime exposure to tobacco smoke before quitting (mean pack-years 39.4). The data provide a refined understanding of the effects of cigarette smoking cessation on erectile dysfunction: smoking cessation in middle age after a significant lifetime exposure to cigarette smoke may fail to modify erectile dysfunction occurrence, because long-term vascular effects of smoking conceivably persist after smoking cessation (Derby et al. 2000b).

Clinical Data

This section examines the link between tobacco exposure and erectile dysfunction, based on objective using various measurement techniques. One widely used early technique to assess arterial vascular competence within the penis was the Doppler ultrasound of arterial pulsations in the flaccid, unstimulated organ. Although this method is no longer applied, the findings of these studies may still be relevant with respect to the pathogenesis of smoking-related vascular

Penile Tumescence Studies

Nocturnal penile tumescence (NPT) monitoring provides a noninvasive diagnostic technique to quantify erection physiology objectively during the naturally occurring cycle of sleep-related penile erections. These spontaneous episodes of tumescence normally accompany rapid eye movement (REM) sleep and are diminished in men with presumably organic erectile dysfunction (Karacan et al. 1978; Allen and Brendler 1992). Several early investigations of the objective basis for vasculogenic erectile dysfunction applied NPT monitoring. Elist and colleagues (1984) confirmed NPT-manifested abnormalities in 20 smokers with erectile dysfunction, among whom 7 (35 percent) displayed normal NPT-manifested results after six weeks of smoking cessation. Virag and colleagues (1985) determined that smokers comprised 72 percent of patients with abnormal NPT results but only 32 percent of patients with normal NPT results. In a study of 168 men who smoked one or more packs per day (heavy smokers) and 632 men who smoked less than one pack per day (light smokers), Karacan and colleagues (1988) found that sleep-related penile erection rigidity was significantly lower at each decade of life after 30 years of age in heavy smokers compared with light smokers, and the duration of maximal tumescence was significantly lower for heavy smokers aged less than 30 years and 51 through 60 years compared with age-equivalent light smokers. In an investigation of 314 smokers with erectile dysfunction, Hirshkowitz and colleagues (1992) confirmed a significant inverse correlation between sleep-related penile erection rigidity and the number of cigarettes smoked per day ($r = -0.12$; $p = 0.04$). These investigators also showed that the duration of maximal tumescence was significantly shorter at the penile base ($p \leq 0.05$), and the duration of detumescence (which refers to the decline from full erection to penile flaccidity) was also shorter ($p = 0.08$) among men who smoked 40 or more cigarettes per day compared with men who smoked 1 to 19 per day and 20 to 39 per day ($p = 0.14$).

Penile Vascular Hemodynamics

Impaired blood flow to the penis can be assessed

disease of the penis. With the values obtained, the penile-brachial index (PBI) can be calculated (the PBI refers to the ratio of penile to brachial systolic blood pressures). Reduced PBI values have been associated with impairment of the erectile process (Kempczinski 1978). Using this technique, Wabrek and colleagues (1983) did not find a significant association between cigarette smoking and abnormal PBI values. Virag and colleagues (1985) also did not find an independent smoking effect on PBI, although a synergistic effect was observed with smoking in combination with other arterial risk factors such as diabetes, hyperlipidemia, and hypertension. In contrast, Candra and colleagues (1986) demonstrated significantly lower PBI values among smokers than among nonsmokers. This same study also noted that the amount of time smoked correlated with abnormal PBI values: smokers with normal PBI values had smoked for a mean duration of 19.95 years while those with abnormal PBI values had smoked for a mean duration of 28.55 years. DePalma and colleagues (1987) likewise found that cigarette smoking carried a significantly higher probability of abnormal (49 percent) than normal (28 percent) vascular laboratory findings including PBI, which was not observed for age, hypertension, diabetes, or prior myocardial infarction. Hirshkowitz and colleagues (1992) confirmed consistent PBI reductions among 314 cigarette smokers with erectile dysfunction, finding significant correlations between the number of cigarettes smoked per day and the magnitude of these reductions for the left dorsal artery ($r = -0.14$; $p = 0.01$) and right cavernosal artery ($r = -0.13$; $p = 0.03$) of the penis.

The vascular evaluation of the penis has more recently employed a pharmacologic stimulus in combination with penile duplex ultrasonography to characterize the penile arteries. This application followed the discovery that a pharmacologic stimulus to induce an artificial erection provides an improved assessment of the physiologic responsiveness of these arteries over that provided during the resting state (Abber et al. 1986). Using this technique and applying a combined set of ultrasonographic parameters to establish normal vascular findings, Shabsigh and colleagues (1991) showed a consistent, nearly statistically significant difference in vascular impairment in smokers compared with nonsmokers. Kadioglu and colleagues (1995) also observed that penile vascular parameters were abnormal to a greater extent among smokers than among nonsmokers, although the differences were not statistically significant.

In summary, PBI testing suggests deleterious effects of smoking on the "resting state" circulation of the penis, and sonographic evaluation of the penis following pharmacostimulation additionally demonstrates apparent deleterious effects of smoking on dynamic blood flow changes in the penis.

Penile Vascular Morphology

Arteriographic studies have been conducted in patients with erectile dysfunction to characterize the vascular anatomy of the penis. Investigations have been carried out among cigarette smokers to confirm the presence and location of arteriographic lesions. Virag and colleagues (1985) calculated a 67.8 percent rate of arteriographic abnormalities among patients in whom organic erectile dysfunction had been established by NPT monitoring, of whom 86 percent were smokers. Bähren and colleagues (1988) similarly showed that 82 percent of their patient group with arteriographically proven peripheral arteriosclerotic lesions were heavy smokers. In a study by Forsberg and colleagues (1989), men with erectile dysfunction underwent screening studies of penile blood flow to identify abnormalities. Using both pharmacostimulation and angiography in 17 men, this study found significant distal penile vessel lesions; 14 (82 percent) of the men were identified as smokers. Rosen and colleagues (1994) carried out a comprehensive evaluation of penile circulation in cigarette smokers with erectile dysfunction, finding that smoking represented a significant independent risk factor in the development of atherosclerotic lesions in the internal pudendal and common penile arteries. These investigators also determined that the number of pack-years smoked was independently associated with hemodynamically significant atherosclerotic disease in the hypogastric cavernous arterial bed supplying the penis (for each 10 pack-years smoked, RR = 1.31 [95 percent CI, 1.05–1.64]).

Histopathology

The effects of cigarette smoking on erectile tissue were investigated by Mersdorf and colleagues (1991), who confirmed degenerative tissue changes, including a decrease in smooth muscle content, sinusoidal endothelium, nerve fibers, and capillaries, and an increase in collagen density) in erectile tissue of smokers. These tissue alterations are consistent with tissue alterations seen in other vascular diseases.

Experimental Data

This section reviews experiments carried out to test the effects of cigarette smoking on erectile function (Table 6.26). These experimental approaches controlled cigarette smoking exposures and provided the possibility for a rigorous evaluation of the consequences for erectile ability. The value of the information was enhanced when experiments involved robust scientific methodology (e.g., a random allocation of people to experimental and control groups, the use of different control groups, and the application of blinding procedures to reduce bias).

Human Studies

Perhaps the first reported study to experimentally evaluate the hypothesized association between cigarette smoking and erectile dysfunction was performed by Gilbert and colleagues (1986), who made polygraphic recordings of penile erection responses in smokers during the viewing of erotic videos. Several aspects of this study are noteworthy: (1) the study population consisted of 42 male self-reported heterosexual cigarette smokers in good health, aged 18 through 44 years; (2) participants were assigned to high-nicotine exposure (0.8 mg nicotine per cigarette smoked), low-nicotine exposure (0.002 mg nicotine per cigarette smoked), or control (sucking on a hard mint candy) groups randomly selected and unknown to the experimenter; (3) at enrollment, a counterdemand was issued to the effect that nicotine enhanced sexual potency, to militate against contaminating hypotheses held by the participants about the effects of smoking on erections; (4) smoking abstention was required for two hours before the experiment; (5) baseline erotic videos were shown for participant acclimation; and (6) concomitant measures of cardiovascular response were obtained. The study found that smoking two, but not one, high-nicotine cigarettes significantly decreased the rate of penile diameter increase compared with the other conditions during the erectile stimulus ($p < 0.001$). It also determined that high-nicotine cigarettes caused significantly more vasoconstriction and heart rate increase than did low-nicotine cigarettes, which did not differ from control conditions ($p < 0.001$).

In another experiment undertaken to assess the acute effects of cigarette smoking exposure on penile erection, Cilina and colleagues (1988) studied the interference of smoking on vasoactive drug-induced erectile responses monitored by intracavernous pressure recording. Study design features were as follows: (1) 12 chronic cigarette smokers, aged 22 through 65 years, were enrolled; (2) subjectively reported erectile function status of the participants at enrollment was not stated; (3) smoking was prohibited on test days; (4) each participant underwent pharmacostimulation consisting of intracavernous injection of 100 mg papaverine hydrochloride at baseline (without smoking) and one week later immediately after nicotine exposure (smoking two cigarettes containing 1.3 mg nicotine per cigarette); and (5) intracavernous pressure measurements were performed 20 minutes following pharmacostimulation by the same experimenter. The study found that all men obtained an erection by clinical judgment at baseline compared with only four (33 percent) after smoking, corresponding to a significant decrease in mean intracavernous pressures (from 85.83 mm Hg at baseline to 33.50 mm Hg after smoking. As part of an earlier, larger investigation of the use of papaverine injections to test diagnostically for erectile dysfunction, Abber and colleagues (1986) described a similar experiment involving a chronic smoker with erectile dysfunction who displayed an acutely worsened erectile response immediately following smoking a cigarette compared with his baseline results.

In a visual depiction of the effects of cigarette smoking on arterial flow to the penis, Levine and Gerber (1989) described their pelvic arteriographic study of a 38-year-old man with a 25 pack-per-year smoking history who presented for evaluation of erectile dysfunction. Whereas a complete baseline evaluation including pelvic arteriographic studies showed no abnormalities, repeat pelvic arteriography immediately after the patient smoked two cigarettes revealed a decrease in the caliber of the entire pudendal artery and nonvisualization of the deep penile artery. The investigators suggested that acute vasospasm was responsible for the observed effects.

Further experimental evidence of the deleterious effects of cigarette smoking on erectile function was recently documented in an acute smoking cessation study by Gray and associates (1998). Ten men, 32 to 62 years of age who had at least a crew 30 pack-year smoking history and were smoking one pack of cigarettes or more per day, were enrolled in a study monitoring NPT and rigidity by a home RigiScan® technique. The study required monitoring of sleep-related penile erections on two successive nights, the first night following a usual day of smoking and the second night following discontinuation of smoking for one 24-hour interval. An additional component of the study involved repeat monitoring in four men who did not smoke for one month although they were administered transdermal nicotine patches (21 mg) during this time. The study results show that erectile parameters improved to a statistically significant degree in men who

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Table 6.26 Experimental studies on the association between smoking and erectile dysfunction

Study	Population	Study design	Stimulus	Outcome
		Human studies		
Gilbert et al. 1986	42 smokers aged 18–44 years	Randomized controlled trial	Visual sexual stimulation	High-nicotine cigarettes reduced the amount of penile diameter increase
[illegible] 1989	12 smokers aged 21–69 years	Acute experimental	Erection plethysmography stimulation	Two cigarettes reduced tumescence pressure and rigidity
[illegible] 1993	153 smokers and 61 nonsmokers	Acute experimental	Sleep-related erections	Report of smoking-erectile dysfunction link; never was this patient's
		Animal studies		
Juenemann et al. 1987	Dogs	Acute experimental	Cavernous nerve electrostimulation	Cigarette smoke inhalation reduced erectile parameters
Xie et al. 1997	Rats	Chronic experiment	Cavernous nerve electrostimulation	Cigarette smoke inhalation did not alter erection parameters

had stopped smoking for 24 hours, with further observed improvements in those not smoking and wearing nicotine patches for one month. The investigators concluded that eliminating cigarette smoking improves erectile function although factors contained in cigarette smoke other than nicotine primarily exert the damaging effects.

Animal Studies

Animal models have provided another useful approach for investigating the association between cigarette smoking and erectile dysfunction. The study by Juenemann and colleagues (1987) using an in vivo canine model represents a comprehensive, well-controlled investigation that combined stimulatory and monitoring techniques relevant to the physiology of erection. The methodology involved monitoring arterial inflow, intracavernous pressure, and venous outflow of the penis during cavernous nerve stimulation of erection alone, and with regulated penile perfusion before and after acute inhalation of cigarette smoke (1.4 mg nicotine per cigarette). Following smoking exposure (one to six cigarettes), compared with nonsmoking baseline conditions, peak arterial inflow was significantly diminished, peak intracavernous pressure was significantly diminished and could not be maintained, and venous outflow was not significantly restricted. Measurable serum nicotine and cotinine levels, obtained in the dogs following smoking exposure and used as markers, were consistent with concentrations found in human smokers, whereas no changes in arterial blood gases or systemic blood pressure were observed throughout the investigation. The investigators concluded that smoking exerts a localized deleterious effect on the neurovascular mechanisms required for penile erection, with a particular impairment of the veno-occlusive mechanism associated with maintenance of penile erections.

In a rat model, Xie and colleagues (1997) evaluated the long-term effects of cigarette smoking on penile erection. The methodology involved monitoring in vivo neurostimulated erections after exposing rats to a constant influx of cigarette smoke in an enclosed cage for a 60-minute session once per day, five days per week, for eight weeks. The investigation surprisingly found increases in intracavernous pressures in

smoke-exposed rats compared with controls. However, the rats exposed to cigarette smoke also developed systemic hypertension. Intracavernous pressures standardized to systemic blood pressures in rats exposed to cigarette smoke did not differ from intracavernous pressures found in controls. The investigators explained their findings on the basis of tobacco smoke-associated vasoconstriction, and they concluded that vascular damage commonly associated with long-term cigarette smoking is inappreciable in the rat model, which is resistant to atherosclerosis.

Evidence Synthesis

Available evidence indicates that cigarette smoking constitutes a risk factor for erectile dysfunction. However, the causal basis for this relationship must be carefully evaluated. With regard to the consistency of the relationship, both case series and population-based studies evaluating rates of erectile dysfunction among smokers provide support. The population-based studies afford a more accurate observational basis for this assessment than do uncontrolled case series, although the paucity of these studies hampers reaching a definitive conclusion. The strength of the relationship also rests on limited available information, but is similarly supported by observational evidence showing that a variety of tobacco exposures (including active and passive cigarette smoking and cigar smoking) is associated with erectile dysfunction. Consideration of a dose-response relationship is supported by a few observational and experimental investigations that have shown an increased risk of erectile dysfunction associated with increased exposures to cigarette smoking. The temporality of the relationship seems likely, with a few observational studies showing some evidence of erectile dysfunction following exposure to tobacco smoke. Intriguingly, preliminary observational findings demonstrate that cigarette smoking cessation apparently leads to a recovery of erectile function only if the discontinuation occurs after a limited extent of lifetime smoking.

Coherence of the relationship is supported by several biologic studies that have proposed plausible mechanisms for the deleterious effects of cigarette smoking on erections. The acute deleterious effects of smoking on erectile function result at least in part from nicotine carried in cigarette smoke. The nicotine pharmacologically induces vasospasm of penile arteries, and hence alters the dynamics of local blood flow required for penile erection. The chronic deleterious effects of smoking on erectile function result from impaired vascular physiology of the erectile tissue, as evidenced by degenerative morphologic changes in tissue of smokers. Although the exact mechanism of the impairment remains unclear, early studies in animals point to damaging effects on tissue-dependent erection regulatory factors. In sum, several lines of evidence contribute toward the inference of a causal relationship between cigarette smoking and erectile dysfunction. However, because the scope of observational and experimental evidence remains limited and incomplete, it seems reasonable to consider the evidence to be suggestive but insufficient to establish a causal relationship at this time.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Implications

The clinical studies and basic scientific research summarized in this section suggest a relationship between cigarette smoking and erectile dysfunction. A strong inference that smoking causes erectile dysfunction requires more evidence to confirm initial findings and to fill in gaps in the knowledge base. Additional observational studies of sufficient size and with well-validated outcome measures are needed. More basic scientific studies to identify biologic mechanisms for the deleterious effects of smoking on penile erections also are necessary. In the meantime, current knowledge about the problem still prompts recommendations for smoking cessation and avoidance to limit the risk of erectile dysfunction. Promoting nonsmoking to prevent erectile dysfunction seems clinically appropriate. There may be significant public health benefits by reducing morbidity rates of this increasingly recognized, widespread condition.

Eye Diseases

Diseases of the visual system, and possible subsequent visual loss, represent substantial social and economic concerns to the U.S. public. In the last three decades, Gallup polls have consistently indicated that blindness is second only to mental incapacity as the disability Americans fear most (National Advisory Eye Council (NAEC) 1998). There is ample reason for concern. An estimated 3.4 million Americans aged 40 years and older have visual impairment and 1 million of these people are legally blind. Because most vision loss results from eye disease associated with advancing age, and the "baby boom" population in the United States is aging, the public health impact of this problem is projected to double by 2030 (Prevent Blindness America 2002).

The economic consequences of eye disease for the U.S. population are huge. For example, sight-restoring cataract surgery was the most frequently performed surgical procedure among Medicare beneficiaries, at an estimated annual cost of $3.4 billion in 1991 (Steinberg et al. 1993). Altogether, the economic impact of visual disabilities and disorders was estimated at more than $38.4 billion in 1995 (NAEC 1998). Thus, substantial contributions to the social and economic welfare of the public are possible by finding and controlling the causes of these eye diseases, particularly the factors that present the opportunity to prevent the disease or loss of sight.

Conclusions of Previous Surgeon General's Reports

Epidemiologic investigation into risk factors for eye disease did not begin in earnest until the 1970s, bolstered by the establishment of the National Eye Institute (NEI) in 1968. Reports of the Surgeon General on smoking and health published before 2001 did not include eye disease as a topic simply because there were scant data indicating that smoking was related to ocular morbidity, although a compelling biologic basis did exist for postulating such associations. At least two of the three leading causes of visual loss worldwide, cataract and age-related macular degeneration (AMD), probably are due, at least in part, to smoking.

Cataract

Cataract is the leading cause of blindness worldwide and a leading cause of visual loss in the United States (Thylefors et al. 1995; Muñoz et al. 2000). Currently, the most common and effective means of restoring vision is through surgical removal of the opacified lens and insertion of an artificial lens into the eye. According to NEI, about 1.35 million cataract operations are performed annually in the United States for Medicare beneficiaries (NAEC 1998), at an estimated cost of $3.4 billion in 1991 (Steinberg et al. 1993). If risk factors that either delay the onset or slow the progression of cataracts could be identified, major socioeconomic gains would be realized. The research findings that link cigarette smoking to cataract, specifically nuclear cataract, have identified one of the few modifiable risk factors for cataract.

The ocular lens is a normally transparent organ having a purely optical function. The lens, situated behind the pupil, focuses radiant energy on the retina to produce an image, much like the lens of a camera. The shape of the lens changes, or accommodates, in response to the distance of the viewed object to focus a sharp image onto the retina.

The transparency of the lens is a function of its peculiar characteristics. The lens itself is composed of a central core, or nucleus, of inert, protein-filled, former epithelial cells. The interior proteins are highly structured to ensure transparency. The lens grows by the constant addition of protein-filled, elongated, former epithelial cells that have differentiated into lens fibers that do not have a nucleus or other organelles. Of interest in this process is that the lens contains every fiber cell ever incorporated into it, including cells formed in the embryo stage through those formed very recently. These cells must maintain transparency throughout the life of an individual to ensure visual clarity, yet this central core is metabolically inert and cannot renew itself. Thus, the central lens is severely restricted in its ability to repair damage. The outermost layer of the lens is composed of a layer of epithelial cells, which are responsible for most of the metabolic activity of the lens. These cells are the source of new cells, as the old cells differentiate into fiber cells and are displaced toward the nucleus. These newest lens fibers make up the lens cortex, which surrounds the nucleus.

The loss of lens transparency is termed lens opacity, and lens opacification becomes increasingly common with advancing age. When the opacity becomes sufficiently dense or extensive or both so as to interfere with vision, the lens opacity is called a cataract. There are three main types of lens opacity or cataract, which are distinct in terms of risk factors, location in the lens, and epidemiologic pattern: nuclear, cortical, and posterior subcapsular lens opacity (West and Valmadrid 1995). The different types of opacities also can occur together in the lens, resulting in a "mixed" opacity.

The frequency of each type of lens opacity in the population increases with age and varies by racial or ethnic group. In one population-based study of 2,520 older Americans (West et al. 1998), aged 65 to 69 years, 32 percent of whites had nuclear, 15 percent had cortical, and 8 percent had posterior subcapsular cataract in at least one eye; comparable figures for African Americans were 20 percent, 42 percent, and 4 percent, respectively. At least 4 percent of the study participants in that age group had undergone cataract surgery as well.

Biologic Basis

Several hypotheses have been advanced to explain a possible association of smoking and cataract. Given the plethora of aromatic compounds and trace metals in cigarette smoke that are capable of damaging lens proteins, it is difficult to know which mechanism is likely to be the most important. Harding (1991) has postulated that cadmium, lead, thiocyanate, and aldehydes from cigarette smoke lead to lens damage. Investigators analyzing blood and lenses from cataract surgery patients have shown significant accumulations of cadmium in the blood and lenses of smokers compared with lenses of nonsmokers, with cadmium in lenses proportional to the amount smoked (Ramakrishnan et al. 1995; Cekic 1998).

Harding (1991) also has suggested that the damage to the lens may be from thiocyanate, which can cause carbamylation of crystallins (lens proteins) and enzymes. Smokers do have elevated thiocyanate levels in their blood, but levels in lenses have not been measured.

Others suggest that smoking may cause cataract through an indirect route, by lowering antioxidants (Taylor et al. 1995). However, the role of antioxidants in protecting against cataractogenesis still is controversial. Few studies have determined the level of antioxidants in the lens and the relationship between lens levels and blood or serum levels. One of the better studied antioxidants is vitamin C, which appears to be concentrated in the lens, and ocular levels of vitamin C are sensitive to plasma levels of this vitamin (Taylor et al. 1997). A review of research linking vitamin C and cataract found studies that reported a protective effect of vitamin C, an increased risk with serum levels of vitamin C, and no association at all; the conflicting results do not provide evidence of an association (West and Valmadrid 1995). In one study, smokers compared with nonsmokers had lower serum values of vitamin C, and in another, both smokers and nonsmokers had similar blood and lens levels of vitamin C (Ralliner et al. 1981; Ramakrishnan et al. 1995). At present, the antioxidant pathway for lens damage from smoking requires more corroborative research.

Epidemiologic Evidence

The relevant articles for this section on eye diseases were identified initially through a search in PubMed from 1966 through 2000 by using the following search terms: "lens opacity," "cataract," "lens," "nuclear lens opacity," "cortical lens opacity," "posterior subcapsular lens opacity," "age-related macular degeneration," "senile macular degeneration," "age related maculopathy," "choroidal neovascularization," "drusen," "geographic atrophy," "atrophic macular degeneration," "diabetic retinopathy," "diabetic eye disease," "glaucoma," "intraocular pressure," "Graves' ophthalmopathy," "thyroidopathy," "eye pathology," and "eye disease." These terms were searched with the Boolean operator "and" followed by the terms "cigarette," "smoking," and "tobacco" in appropriate combinations. All articles were reviewed, and their bibliographies were reviewed for relevant articles not captured by the search strategy. The final selection of articles for citation in this section was made in consideration of the adequacy of the research or review and the relevance to the topic. The selection of eye diseases for review was based on the public health importance of the disease and the availability of research relevant to an association with smoking.

Several key methodologic issues should be addressed in any research on risk factors for cataract. First, there are different types of cataract, with largely unique risk factors for each type. Early research on risk factors often did not differentiate cataract type, making interpretation difficult because the role of cataract types was unknown. For example, a surgical series of cataract patients is likely to be heavily weighted for posterior subcapsular cataract, whereas a population-based series will have few posterior subcapsular cataract cases. Surgical notes, or ophthalmologic

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notes, of the cataract type may lead to misclassification, as only the major cataract type usually is recorded. Ideally, studies on cataractogenesis would use one of several reliable, valid grading schemes for documentation of the presence and severity of lens opacity types.

The second methodologic issue is that each type of lens opacity has a different impact on the visual system. Research that defines cataract to include a visual acuity criterion effectively excludes asymptomatic, early lens changes or may include substantial numbers of persons with lens opacity but yet affecting acuity in the control group. Such research is less desirable from an etiologic standpoint.

Finally, issues of bias and confounding must be addressed with any research. Selection bias in clinic-based [illegible] control studies of cataract can be problematic because controls sometimes have eye problems that may be risk factors in common with cataract. In population-based studies, patients with bilateral cataract surgery often are excluded from the analyses, because the type of cataract or date of surgery may be unknown. If the risk factor of interest drives progression of cataract, the exclusion of bilateral surgical cases will result in an underestimation of the risk. Potential confounders for the relationship of smoking and nuclear or posterior subcapsular cataract include age, race, gender, steroid use, and possibly alcohol use.

Ten epidemiologic studies reviewed have found an association between smoking and nuclear opacity and four found an association between smoking and posterior subcapsular opacity (Table 6.27). The studies reporting an association between nuclear cataract and smoking were carried out in diverse populations using different methodologies and different lens grading systems (Klaye et al. 1989; West et al. 1989a, 1995; Leske et al. 1991, 1998; Christen et al. 1992; Hankinson et al. 1992; Klein et al. 1993b; Cumming and Mitchell 1997; Hiller et al. 1997). The association with smoking generally was consistent (with most RRs ranging between 2 and 3); a dose-response relationship with the amount smoked was found. Four prospective cohort studies have found an association with smoking at baseline and subsequent risk of developing new nuclear opacities, surgery for nuclear opacities, or progression of existing nuclear opacities (Christen et al. 1992; West et al. 1995; Hiller et al. 1997; Leske et al. 1998).

Smoking has been less consistently associated with an increased risk of posterior subcapsular opacity. Two prospective cohort studies have found an increased risk, between 2.5- and 3-fold, associated with heavy smoking (smoking 20 or more cigarettes per day and smokers of 65 or more pack-years) (Christen et al. 1992; Hankinson et al. 1992). Two cross-sectional, population-based studies found a weaker association, and one reported an association only among men (Klein et al. 1993b; Cumming and Mitchell 1997). Two other population-based surveys did not find any association with posterior subcapsular cataract (Klaye et al. 1989; Hiller et al. 1997).

One limitation of population-based studies of risk factors for posterior subcapsular cataract is the rarity of that cataract type, making it difficult to acquire enough cases to precisely characterize risk. Another limitation is that posterior subcapsular cataract is highly visually disabling, and generally progresses quickly, so while it is overrepresented in surgical series it may be underrepresented in population-based studies because affected persons already have had cataract surgery (West et al. 1988). Thus, prospective cohort studies on posterior subcapsular cataract in populations are likely to provide more compelling data about the association.

The three studies that found no association between smoking and cataract deserve comment. The case-control study in India (Mohan et al. 1989) was hospital-based and relied on patients from one center. The possibility of selection bias, especially in terms of cases with vision loss and controls without vision loss and their COPDs, must be considered. The case-control study in Italy (Italian-American Cataract Study Group 1991) had a design similar to the study in India but used cases and controls from three clinics covering the population in Parma, Italy. This broader coverage reduced the possibility for selection bias. However, the recruitment rates of cases of posterior subcapsular cataract and nuclear cataract were lower than expected; the smoking data were not shown for this study, so an assessment of the power to detect an increased risk associated with smoking could not be done. The third study (Bochow et al. 1989), a case-control study of risk factors for posterior subcapsular cataract, did not evaluate the association of smoking with other cataract types. The controls included patients with nuclear cataract alone or with AMD, which may have increased the prevalence of smoking in the comparison group. Thus, the three studies that did not find an association between smoking and cataract have limitations that may have introduced bias toward the null.

There are no clinical trials of smoking cessation and determinations of either reduced risk of onset or progression of lens opacities. Six studies examined

the risk in former smokers, and the data in general support a lower risk of progression or development of cataract after cessation. The mechanism is likely to be a reduction in the smoking-related dose of injurious agents to the lens rather than any reversal of the cataractogenic process. A cross-sectional survey looked in detail at time since smoking cessation and reported that cessation of 10 or more years reduces the risk of nuclear opacity (West et al. 1988a). In two large prospective cohort studies, former smokers at baseline had no increased risk of new nuclear opacities (Christen et al. 1992) or new cataract surgery (Hankinson et al. 1992). The 13-year follow-up study among male physicians of self-reported development of visually significant cataract found a lower risk among former smokers compared with current smokers (Christen et al. 2000). The prospective data are compatible with previous work showing that ongoing smoking drives progression. Other researchers who found similar risks for former smokers as for current smokers did not evaluate risk by years since cessation (Cumming and Mitchell 1997; Hiller et al. 1997). Studies of risk for cataract among smokers using low-yield cigarettes or low-tar products have not been reported.

Evidence Synthesis

Substantial evidence based on cross-sectional and prospective cohort studies now has accrued linking nuclear, and possibly posterior subcapsular, cataract to cigarette smoking. There is a dose-response relationship and evidence that former smokers have a lower risk of cataract and of progression of cataract compared with current smokers. On the basis of the epidemiologic studies, researchers now are investigating the mechanisms by which smoking may damage the lens, by using animal and lens cell culture models. The laboratory data are not yet sufficiently mature to inform the discussion of smoking and cataract. In part because there are few animal models of age-related cataract, most require an external insult to initiate the cataractogenic process. However, smokers are exposed to a number of agents that may cumulatively damage the lens, which lacks reparative capacity.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.
2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

Implications

There is moderate evidence to suggest that smoking also may be associated with an increased risk of posterior subcapsular opacities as well, but more research is needed before a causal association can be inferred for this cataract type. The difficulty the lens has in repairing damage suggests that opacification at the time of smoking cessation is likely to be irreversible. Studies of cataract in clinical trials of smoking cessation would provide more definitive evidence for any protective effect, although feasibility would be constrained by the need for large populations.

Age-Related Macular Degeneration

AMD is the leading cause of blindness in whites aged 65 years and older in the United States (Sommer et al. 1991; Muñoz et al. 2000). There currently is no well-accepted treatment to prevent or halt the progression of atrophic AMD, the most common form of AMD. Treatment to halt vision loss from the less common, severe form of AMD, exudative (neovascular) AMD, often is short lived, as neovascularization (new blood vessel formation) often recurs. A recent large-scale clinical trial has provided evidence that antioxidant supplements plus zinc may delay the progression of some signs of AMD (Age-Related Eye Disease Study Research Group 2001). Otherwise, no preventive therapy for AMD is available, so considerable attention has focused on identifying risk factors for this disease.

The macula is a component of the retina at the center of the optical axis; it contains the fovea, a highly specialized area of the retina responsible for high-resolution vision. The retina consists of neural tissues, including the photoreceptors that convert energy from visible light into electrical signals sent on to the brain for processing. The photoreceptors—rods and cones—have high metabolic requirements and replace their outer segments daily. The metabolic functions of the retina are supported by the retinal pigment epithelium, which phagocytizes an estimated 2,000 outer segment membranes daily. This high rate of activity is made possible by the exchange of nutrients (and removal of waste) through the retinal blood supply, the choriocapillaris. There is a blood retinal barrier to this exchange, which is formed by both the retinal pigment epithelium and its anchor, Bruch's membrane (lamina basalis choroideae). Thus, the complex of the retinal pigment epithelium, Bruch's membrane, and the choriocapillaris serve as the nutritional source for the

sensory retina. Changes in each of the tissues in this complex have been hypothesized to result in AMD. However, the pathogenesis of AMD, indeed the differentiation of changes in early AMD from those of normal aging, is uncertain (Sarks and Sarks 1994).

AMD is an umbrella designation for a variety of degenerative changes in the macula. The degeneration is characterized in its early stages by pigmentary disturbances and atrophic changes. The late stages of AMD are characterized by widespread atrophy of the retinal pigment epithelium, loss of photoreceptors (atrophic AMD), and, less commonly, exudative AMD. With exudative AMD, new, unstable blood vessels develop in the choroid and grow under or through the retinal pigment epithelium via breaks in Bruch's membrane. Leakage from these neovascular membranes may lead to detachment of the retinal pigment epithelium, hemorrhage, and formation of a disciform scar. The late stages are associated with vision loss, classically loss of central vision, the part of vision responsible for activities such as reading and close work.

Morphologic changes associated with AMD include basal laminar deposits at the level of the retinal pigment epithelium, thickening of Bruch's membrane, and drusen. Drusen are deposits of extracellular material thought to be accumulations or "garbage bags" of waste products from the retinal pigment epithelium. At least two types of drusen are recognized clinically on the basis of their appearance: small, hard drusen, which are a common feature of aging; and larger, soft drusen, which also are common with aging but are a likely risk factor for developing severe AMD. The presence of drusen in the fundus, thought to be the hallmark of early AMD, is being challenged as a marker by observations that drusen can appear and disappear over time (Bressler et al. 1989; Klein et al. 1997), that most people with large, soft drusen do not develop advanced AMD (Klein et al. 1997), and that epidemiologic patterns associated with advanced AMD are different from those for drusen-defined early AMD. This debate has relevance in evaluating the evidence for an association of smoking and early versus advanced AMD.

Biologic Basis

Of the postulated mechanisms underlying the retinal changes in AMD, three have bearing on the hypothesis that smoking is associated with AMD. The first can be characterized as oxidative stress leading to changes in the ability of the retinal pigment epithelium to phagocytize cellular products, which in turn leads to accumulations of debris that interfere with the nutrient exchange between the retinal pigment epithelium and the choriocapillaris. Oxidative stress can result from free-radical damage to proteins, lipids, and possibly, mitochondrial DNA. The stress is considered to contribute to malfunctions of the retinal pigment epithelium. The macula is a particularly likely target for oxidative stress because of the macula's high exposure to light, high metabolic rate, and high concentrations of fatty acids. But the macula also is very rich in antioxidative, protective mechanisms, including an array of antioxidant nutrients and enzymes, as well as melanin. Smoking, through its actions on reducing plasma levels of antioxidants in addition to reducing macular pigment, is hypothesized to increase the oxidative stress on the macula by robbing it of its defenses (Hammond et al. 1996).

The second hypothesis for the pathogenesis of AMD proposes that the degradation of Bruch's membrane, as manifested by thickening and changes in the composition, leads to interference with nutrient exchange between the retinal pigment epithelium and its blood supply. Vascular endothelial growth factor (VEGF) has been reported in the retinal pigment epithelium cells; these cells may liberate VEGF in response to the interference in nutrient exchange. Investigators are working on the role of VEGF, released in connection with hypoxia, in the pathogenesis of AMD, particularly for the neovascular type (Mousa et al. 1999). Smoking has been associated with an increase in plasma immunoreactive VEGF, at least acutely, operating likely through its ability to cause tissue hypoxia (Wasada et al. 1996).

The third hypothesis for the pathogenesis, or at least a possible contributing cause, of AMD is vascular insufficiency. Changes in the choroidal circulation may impair the ability of the retinal pigment epithelium in disposal of waste substances, leading to the accumulation of waste material. The rate and volume of blood flow through the choriocapillaris are high in response to the demands of the pigmented epithelium and the photoreceptors. Smoking has been shown to alter choroidal blood flow (Bettman et al. 1958). Smoking also affects the vasculature through platelet adhesions and hypoxia from elevated levels of carboxyhemoglobin, which might add to the stimulation of new vessel growth.

It is likely that multiple pathways are responsible for the degenerative changes in the macula with age, and a reasonable basis exists for presuming that smoking may operate through one or more of these pathways.

Table 6.27 Studies on the association between smoking and cataracts

Study	Population	Design
	Association found	
Clayton et al. 1982	931 cataract surgery patients and controls	Case-control
[illegible]	[illegible] persons with cataracts	[illegible]
Harding and Hey[illegible]	[illegible] cataract surgery patients and controls	[illegible]
Klaye et al. 1989	1,900 persons with cataracts	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
West et al. 1989a	668 male fishermen	Cross-sectional
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
Christen et al. 1992	5,823 male physicians without self-reported cataracts at baseline	5 [illegible]

[illegible] = illegible

[a] Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[b] OR = Odds ratio.
[c] CI = Confidence interval.
[d] RR = Relative risk.

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Cataract assessment	Results
No type specified; surgical cases	Heavy smoking was twice as common in cases; no data were reported; confounding was not addressed
Clinical examination, type	Smoking was associated with nuclear opacities; data not [illegible]
No type specified; surgical cases	[illegible] associated with cataract surgery [illegible]
Clinical examination, nuclear, cortical, and posterior subcapsular opacities	[illegible]
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	The [illegible] years and risk of nuclear opacities, p <0.004 (too few posterior subcapsular opacities to analyze); risk declined if participants had stopped smoking for ≥10 years; adjusted for age and gender
Photographs for nuclear, cortical, and posterior subcapsular opacities; Lens Opacities Classification System II used	No [illegible] current [illegible] there [illegible] type and [illegible] duration [illegible] confounders
Self-reported development of cataracts; medical records for date of diagnosis, date of extraction, type, and loss of vision	76 of current smokers of ≥20 cigarettes/day, RR = 2.74 for nuclear (95% CI: 1.47–3.41) and 3.17 (95% CI: 1.81–5.53) for posterior subcapsular cataracts; there was no association with <20 cigarettes/day; former smokers had no increased risk of nuclear or posterior subcapsular cataracts; adjusted for confounders

Table 6.27 Continued

Study	Population	Design
	Association found	
Hankinson et al. 1992	50,828 female nurses without self-reported cataracts at baseline	Approximately 8-year prospective
Klein et al. 1992a	Population-based sample of 4,926 [illegible]	Cross-sectional
West et al. 1995	442 male fishermen with photographs 5 years apart	5-year prospective for incidence and progression
Cumming et al. Mitchell 1997	Population-based sample of 3,654 adults	Cross-sectional
Hiller et al. 1997	660 members of Framingham Eye Study with no lens opacities	4-year prospective
Leske et al. 1998	Total of 4,561 participants [illegible]	4-year progression of lesser [illegible]
Christen et al. 2000	20,595 male physicians with no cataracts at baseline	12-year prospective

Cataract assessment	Results
Self-reported cataract extractions, medical records for type	Smokers of 65 pack-years had increased risks for nuclear cataracts, RR = 1.79 (95% CI, 0.83–3.88), and posterior subcapsular cataracts, RR = 2.59 (95% CI: 1.59–4.59) for current smokers. Few cases of nuclear cataract [illegible] former smoking had no increased risk un[illegible]ey had smoke[illegible]5 cigar[illegible]/day[illegible]sted fo[illegible]or
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	[illegible] Study, OR [illegible] 1.12, [illegible] smoking [illegible] women, OR = [illegible] were also assessed, adjusted for confounders
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	[illegible] [illegible] 1.05–3.63, 1.15–3.80) for progression of nuclear opacity, which was associated with the number of [illegible] year smoking, OR = 1.18 (95% [illegible] 1.02–1.36) per 5 years. In 1 pack-year increments, adjusted for baseline severity and age, there was no association with incident nuclear opacity
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	Former smokers had increased ORs for incident nuclear opacity, OR = 1.39 (95% CI, 1.11–1.68) and posterior subcapsular opacity, OR = 1.5 (95% CI, 1.22–2.0). Men were at [illegible] risk than women; [illegible] smokers for [illegible] quitting was associated with [illegible] risks
Clinical examination, nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	Light smokers [illegible] were associated with [illegible] nuclear opacity, OR = 1.68 (95% CI, 1.14–2.49) [illegible] as heavy smoking, OR = 2.37 (95% CI: 1.43–3.93); former smokers (but could be [illegible] and [illegible]) had an increased risk of incident [illegible], OR = 2.02 (95% CI, 1.14–3.57); [illegible] both [illegible] were
Photographs for nuclear, cortical, and posterior subcapsular opacities; Lens Opacities Classification System II used	The [illegible] with [illegible] 1.05–2.16) [illegible] other [illegible] of cataract
Self-reported development of cataracts; medical records with dates of diagnosis and extraction, and loss of vision (type not specified)	Former smokers had a lower risk of cataract surgery (type not specified) compared with current smokers, and a lower risk of cataract surgery, adjusting (for number of cigarettes smoked and other confounders, RR = 0.78 [illegible] CI, 0.67–0.92)

Table 6.27 Continued

Study	Population	Design
	No association found	
Bochow et al. 1989	Posterior subcapsular cataract cases and controls	Case-control
Italian-American Cataract Study Group 1994	1,078 [illegible] cases [illegible]	Case-control
Mohan et al. 1989	1,341 [illegible] in India with cataract [illegible] 749 controls	Case-control

Epidemiologic Evidence

Two methodologic issues add to the complexity of assessing the relationship between AMD and smoking. The first issue is that advanced, or severe, AMD mostly occurs in the very old. About 7 percent of the white population aged 75 years and older will have advanced AMD (Klein et al. 1992). The second issue is that life expectancy of smokers is less than that of nonsmokers, so selective survival of smokers to even develop AMD is an issue. Together, the relatively low incidence of AMD and the low prevalence of smoking in very elderly populations diminish the power to detect associations in all but the largest studies, which is evident in the population-based studies of AMD that have low numbers of cases of severe AMD.

One way to circumvent the problem is to study the association of smoking in precursor lesions or early AMD; however, there is no uniform agreement on the clinical signs of early AMD. Many of the signs currently in use are common in the population and can be so unstable as to be almost uninformative about who will develop advanced AMD. Data are accumulating on predictors of advanced AMD, the presence of very large drusen, and the retinal area covered by drusen. In part, the difficulty of determining the relevant early signs may be due to the limitations of photographic systems to detect such changes in, for example, Bruch's membrane; for research purposes, however, no alternative detection systems are available for accurately detecting early changes.

With these caveats in mind, the research findings to date suggest a strong likelihood that smoking is related to advanced or severe AMD, particularly exudative AMD, but there is scant evidence that smoking is related to the apparent early signs of AMD (Table 6.28). One cross-sectional, population-based study (Smith et al. 1996) found increased odds of early AMD among smokers compared with nonsmokers (OR = 1.88 [95 percent CI, 1.25–2.84]). However, two others, using identical grading methods, found no increased odds (Klein et al. 1993c; Delcourt et al. 1998). In another cross-sectional survey of fishermen who were heavy smokers, a paradoxical protective effect was seen for smoking and the odds of early AMD, primarily cases of moderate drusen (West et al. 1998b). A prospective cohort study of the risk of developing early signs of AMD found an increased risk of developing large (≥250 μm) drusen among smokers compared with lifetime nonsmokers; the RR was 3.21 (95 percent CI, 1.09–9.45) among men and 2.20 (95 percent CI, 1.04–4.66) among women. No other early sign was associated with smoking (Klein et al. 1998). The lack of association with presumed early AMD may be due to the imprecision of the signs chosen to represent early AMD, thus biasing the results toward the null. Further work on improving this classification is warranted. It is also possible that smoking is related to progression of AMD to the exudative form but not to the onset of early lesions.

Gender differences appear in the findings as well. In one case-control study of severe AMD, the relationship with smoking was observed in men only (Hyman et al. 1983). In one prospective cohort study in a population having primarily early AMD, progression of AMD among smokers was observed with a dose-response pattern only among men (Klein et al. 1998).

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Cataract assessment	Results
Chart reviews for and absence of posterior subcapsular cataracts	Current and former smoking were not related to [illegible] or subcapsular cataracts
[illegible]	[illegible] duration of smoking or pack-years of smoking
Nuclear, cortical, and posterior subcapsular cataracts on clinical exam; no grading scheme described	Compared new A-[illegible] and current smokers among cases and controls; no differences were reported (data were not shown)

A prospective cohort study of exudative AMD among men found a benefit of quitting smoking after 20 years of cessation (Christen et al. 1996), but a similar study among women found no benefit after 15 or more years of cessation (Seddon et al. 1996). There are not evident explanations for these differences, except that the significantly lower prevalences of smoking among women may reduce the power to detect associations with AMD, especially if heavy smoking is the risk-determining factor.

The strongest and most consistent association seen in the literature is the association of current smoking and risk of severe AMD, especially exudative AMD. Because several studies tended to combine atrophic and exudative AMD into "late" or "severe" AMD, it is difficult to know whether to attribute the association to either one or both, unless specified. Four case-control studies have been reported to date. A large case-control study of exudative disease (Eye Disease Case-Control Study Group 1992) found an increased OR with current and past smoking of 2.2 (95 percent CI, 1.4–3.5) and 1.5 (95 percent CI, 1.2–2.1), respectively. Three other case-control studies also found an increased risk for severe AMD in smokers, with estimated ORs between 2 and 3 (Hyman et al. 1983; Macular Photocoagulation Study Group 1996; Tamakushi et al. 1997). Four cross-sectional, population studies found increased odds of exudative AMD among current smokers, with ORs between 1.5 and 3.6; two of the four studies found a dose-response relationship. Two of the four cross-sectional studies found increased odds of atrophic AMD with current smoking (Vinding et al. 1992; Smith et al. 1996), but the other two did not (Klein et al. 1993c; Vingerling et al. 1995). Two prospective studies found a significant association with either exudative disease or severe AMD in current heavy smokers (20 or more cigarettes per day) (Christen et al. 1996; Seddon et al. 1996). Former smokers also had an increased risk of AMD, although lower than that for current heavy smokers. Quitting more than 20 years previously appeared to decrease the risk in two cross-sectional studies (Vingerling et al. 1995; Delcourt et al. 1998), as well as in a prospective cohort study in men (Christen et al. 1996). In the prospective study in women (Seddon et al. 1996), however, quitting 15 or more years prior did not decrease the risk of severe AMD.

The data from cross-sectional studies suggest that passive smoking is not related to early or late AMD (Klein et al. 1993c; Smith et al. 1996). There are no corroborating data from animal models. Although animal models of induced retinal damage exist, no good animal models present the spectrum of features of AMD.

Evidence Synthesis

These data provide evidence that current smoking is associated with exudative AMD and possibly atrophic AMD. Dose-response relationships with the amount of smoking have been described. Maintaining smoking cessation at least 20 years decreased the risk of severe AMD and exudative AMD. The possibility that smoking is associated with the neovascular form of AMD is further bolstered by the findings from a study of ocular histoplasmosis (Ganley 1973), where

neovascularization can result from the infection. In that study, smokers were twice as likely as nonsmokers to develop disciform scars. Moreover, in a clinical trial of photocoagulation to halt progression of neovascularization, smokers were more likely than nonsmokers to have recurrent neovascularization over time (Macular Photocoagulation Study Group 1986). However, smoking did not predict development of neovascularization in the previously unaffected companion eyes of the eyes with neovascularization (Macular Photocoagulation Study Group 1997).

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

Implications

There is a need for more research into gender differences, dose-response relationships, and a possible threshold effect. Further research is also needed to determine the effect of smoking cessation on the risk of neovascular AMD.

Diabetic Retinopathy

Diabetic retinopathy is a serious ocular complication of diabetes associated primarily with long-term duration of diabetes and poor control in both type 1 and type 2 diseases. The retinopathy is likely the result of vascular changes occurring in the retinal circulation that feeds the inner layers of the retina. Diabetic retinopathy in the early stages (mild, non-proliferative retinopathy) is characterized by excessive permeability of the vasculature, with ballooning of the retinal capillaries to form microaneurysms, dot hemorrhages, and hard and soft exudates. Preproliferative retinopathy includes, in addition to the aforementioned features, vascular occlusion and dilation and/or venous beading. Proliferative diabetic retinopathy is characterized by new vessel growth or fibrous proliferation or both. Vitreous hemorrhage secondary to the neovascularization also may be seen. Clinically significant macular edema, the result of extensive vessel leakage, can be a feature of chronic diabetic eye disease that may occur at any stage of the process. The prevalence of diabetic retinopathy increases with duration of diabetes, and most persons with diabetes have signs after 10 years' duration. Moreover, diabetic retinopathy is an important cause of vision loss. Although photocoagulation is an effective means of treating proliferative diabetic retinopathy, too often the retinopathy is not diagnosed at an early stage when treatment can be maximally effective.

Biologic Basis

Several investigators have postulated that smoking may contribute to the onset of diabetic retinopathy and/or drive progression of existing retinopathy through its effect on the retinal circulation (Morgado et al. 1994). If such relationships exist, one mechanism of action is likely to be hypoxia from chronic exposure to carbon monoxide, which may be toxic to retinal vasculature. Carbon monoxide also is associated with separation of arterial endothelial cells, causing edema, which also is a feature of diabetic retinopathy. Nicotine exposure increases levels of plasma vasoconstrictors, such as angiotensin and vasopressin, which have binding sites on retinal blood vessels. In addition, nicotine exposure increases platelet adhesiveness, and persons with diabetic retinopathy are more likely to have increased platelet aggregation compared with persons with diabetes but without retinopathy. Although there is a reasonable biologic basis to the hypothesis that smoking is related to diabetic retinopathy, the data suggest otherwise.

Epidemiologic Evidence

Many studies have examined the association between smoking and diabetic retinopathy (Table 6.29), and the data from several studies do not support the proposed association. The well-controlled studies, including prospective cohort studies in large populations of persons with diabetes, found no association between smoking and the amount smoked and the prevalence, incidence, or progression of diabetic retinopathy (Klein et al. 1988; Moss et al. 1991, 1996). Studies that found an association in general did not adjust for level of control of diabetes, a major risk factor for diabetic retinopathy. One study did adjust for level of control and other risk factors and found an

association between smoking and a six-year progression of diabetic retinopathy (Muldhauser et al. 1998). However, progression was defined as any progression from onset of diabetic retinopathy to becoming blind, if proliferative diabetic retinopathy was present at baseline. There were no data shown on whether smokers tended to have worse retinopathy at baseline, but the analyses should have adjusted for baseline status of diabetic retinopathy as a risk factor for progression. When the progression was confined to the subgroup with no retinopathy at baseline, smoking was not significantly associated with either the incidence or progression of diabetic retinopathy.

Evidence Synthesis

Although smoking might plausibly worsen diabetic retinopathy, the evidence is inconsistent. The strongest studies, the prospective cohort studies, do not show an association. The level of diabetes control is a potential major confounder that has not been considered in a number of the studies.

Conclusion

1. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

Implication

As research on diabetes continues, possible effects of smoking should be reassessed.

Glaucoma

Glaucoma is the third leading cause of blindness worldwide (Thylefors et al. 1995). In the United States, African Americans and Hispanics are more affected than other groups. Glaucoma is a disease characterized by loss of retinal ganglion cells, probably through a variety of mechanisms. The two main types of primary glaucoma are primary open-angle glaucoma and angle closure glaucoma. The angle refers to the angle between the iris and trabecular meshwork in the anterior chamber, which if shallow or closed impedes outflow of aqueous fluid and causes a rise in pressure. There are distinct differences between the two types of glaucoma, and their distribution differs in populations. In the United States, primary open-angle glaucoma is the more common type.

Biologic Basis

There is no evident basis for proposing that smoking might predispose a person to either developing glaucoma or having more severe glaucoma. Investigators have proposed that factors that diminish perfusion of the optic nerve head with blood may be associated with glaucoma. Because smoking affects the retinal circulation (although any direct effect of smoking on the optic nerve head is unknown), several investigators have examined the association of glaucoma with smoking. However, the effects of smoking on blood flow in ocular circulation are difficult to measure. In part because studies often do not consider separating acute effects in smokers and nonsmokers from the chronic effects that result from repeated exposures, the role of smoking in altering intraocular pressure also is variable. In one study (Shephard et al. 1978), smoking (including cumulative consumption) was not associated with intraocular pressure differences.

Evidence Synthesis

The few epidemiologic studies conducted (Table 6.30) do not indicate any relationship between smoking and glaucoma. Three cross-sectional studies found no association between smoking and glaucoma (Klein et al. 1993a; Ponte et al. 1994; Leske et al. 1995), and one prospective cohort study found no increased risk of glaucomatous field loss among persons with ocular hypertension who smoked compared with those who did not smoke (Quigley et al. 1994). The association has not been evaluated in angle closure glaucoma, but there is little biologic basis for proposing such a relationship.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

Implication

As further studies of glaucoma are undertaken, the role of smoking should remain under investigation.

Table 6.28 Studies on the association between smoking and age-related macular degeneration (AMD)

Study	Population	Design
Paelkau et al. 1978	114 cases of exudative AMD from 1 clinic	Cross-sectional
McDonnell et al. 1979	[illegible] AMD [illegible]	[illegible]
Hyman et al. 1983	[illegible] AMD and [illegible]	Case-control
Blumenkranz et al. 1986	[illegible] AMD [illegible]	[illegible]
Macular Photocoagulation Study, Group 1996	[illegible] AMD [illegible]	[illegible] ective
Mitchell et al. 1997b	[illegible] AMD [illegible]	[illegible]
Eye Disease Case-Control Study, Group 1992	AMD [illegible]	[illegible]
Vinding et al. 1992	Population-based, samples of [illegible] persons in Copenhagen aged 50 years; [illegible] AMD in 2.4% of [illegible] AMD	Cross-sectional
Klein et al. 1993c	Population-based sample of 4,771 participants aged ≥43 years; 41 cases of exudative AMD and 29 of atrophic AMD	Cross-sectional

[illegible]OR = Odds ratio.
[illegible]CI = Confidence interval.
[illegible]RR = Relative risk.

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AMD assessment/type studied	Results
Fluorescein angiography	Current smokers had an earlier age of onset of vision loss ([illegible] years) compared with nonsmokers (71 years), [illegible]
[illegible]	[illegible] percent with AMD reported smoking at some point, compared with 7 percent with no association [illegible]
[illegible]	Male smokers were [illegible]
[illegible]	Smokers were [illegible]
[illegible]	[illegible] studied
Fundus photographs; Beginning AMD	Ever smokers had [illegible]
Ophthalmologic examination and fundus photographs; Beginning AMD with vision loss	Current smoking was associated with neovascular AMD; OR = 2.2 [illegible] former smokers also had a [illegible]
Ophthalmologic examination and fundus photographs; Early and late AMD with vision loss	Both atrophic OR = 1.5 [illegible] and exudative OR = 1.5 [illegible] small to [illegible] AMD cases were examined, [illegible] found in small [illegible]
Fundus photographs; Early AMD using grading scheme used for early and late AMD	There was no relationship of early AMD (drusen characteristics, pigmentary disturbances) to smoking status, dose, or passive smoking; current smokers had a higher frequency of exudative AMD, OR = 2.5 (95% CI, 1.01–6.3) among women and 3.29 (95% CI, 1.03–10.5) among men; it was not associated with passive smoking; a dose-response pattern was reported only for women; there was no association with atrophic AMD

Table 6.28 Continued

Study	Population	Design
Christen et al. 1996	21,157 male physicians aged ≥40 years with no AMD at baseline, followed for ≥7 years; 268 had AMD with vision loss and 64 had exudative AMD	Prospective
Seddon et al. 1996	[illegible] with no AMD at baseline; [illegible] 2 to 12 years; 217 had AMD with vision loss, 67 had exudative AMD	Prospective
Smith et al. 1996	Population-based [illegible] participants aged ≥55 years; 50 cases of exudative AMD and 74 of atrophic AMD	Cross-sectional
Vingerling et al. 1995	Equally [illegible] of 5,771 participants aged 55 years; [illegible] of neovascular AMD and 90 cases of atrophic AMD	Cross-sectional
Yamamoto et al. 1997	56 cases of exudative AMD among Japanese men aged 50–69 years in 5 hospitals; 82 male controls with no macular changes (coming for physical exam)	Case-control

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

AMD assessment/type studied	Results
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist	Current smokers of ≥20 cigarettes/day had an increased risk of AMD with vision loss, RR = 2.57 (95% CI, 1.70–3.90); there was no increased risk with smoking <20 cigarettes/day, RR = 1.18 (95% CI, 0.57–2.42); former smokers had an increased risk, RR = 1.30 (95% CI, 1.01–1.69); dose–response relationship was present; quitting for ≥20 years decreased the risk; current smokers (no dose was given) had an increased risk of exudative AMD, RR = 1.96 (95% CI, 0.91–4.24); no increased risk with former smoking; cases of AMD without vision loss had no association with smoking
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist; cases confirmed by fundus photographs	Current smokers [illegible] increased risk of AMD with vision loss, RR = [illegible] 2.57 cigarettes/day, RR = 2.4 (95% CI, 2.0–4.0), [illegible] an increased risk, RR = 3.8 (95% CI, [illegible] dose–response relationship was present; [illegible] had RRs [illegible] current smokers were [illegible] having stopped smoking for ≥20 years, there was [illegible] AMD among nonsmokers
Fundus photographs; Grading scale: Wisconsin grading scheme for early and late AMD	Current smokers had a higher [illegible] neovascular AMD, OR = 3.20 (95% CI, 1.49–7.33); atrophic AMD, OR = 4.3 (95% CI, 1.2–15.82); and early AMD, OR = [illegible] ORs were elevated for neovascular and atrophic AMD, but not significantly for [illegible] smoking was not associated with any AMD; there were no associations between [illegible] AMD and pack-years[1]
Fundus photographs; Grading system: Wisconsin grading system	Current smokers [illegible] had an increased prevalence of [illegible] AMD, OR = [illegible] (95% CI, 1.8–7.8); [illegible] exhibited a dose–response relationship, OR = [illegible] (95% CI, [illegible]); [illegible] stopping smoking for ≥20 years, the risk [illegible] AMD among nonsmokers
Fundus photographs and fluorescein angiography	Nearly [illegible] with current smoking, OR = 3.67 (95% CI, 1.98–8.63), and former smoking, OR = 2.89 (95% CI, 0.71–6.13); a dose–response relationship was present, with a high risk for those who started smoking before 20 years of age, OR = 3.41 (95% CI, 1.29–9.73)

Table 6.28 Continued

Study	Population	Design
Delcourt et al. 1998	2,196 participants aged ≥60 years in a population-based survey; 41 cases of late AMD (neovascularization or geographic atrophy)	Cross-sectional
Klein et al. 1998	[illegible] years [illegible] a long-[illegible] population-based study reported [illegible] incidence of [illegible] exudative AMD	5-year prospective

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AMD assessment/type studied	Results
Fundus photographs graded according to Wisconsin grading system	Current smoking, OR = 3.5 (95% CI, 1.0–12.2), and former smoking, OR = 2.8 (95% CI, 1.1–6.9), were associated with late AMD (not further separated into atrophic vs. neovascular AMD); dose-response relationship was present; those who stopped smoking within 20 years had the same risk as current smokers; there were no associations with early AMD
Fundus photographs graded according to Wisconsin grading system	Current [illegible] 95% CI [illegible] RR [illegible] 95% [illegible] relative [illegible] [illegible] [illegible] patients

Table 6.29 Studies on the association between smoking and diabetic retinopathy (DR)

Study	Population	Design
Paeifkau et al. 1977	150 cases of diabetes	Cross-sectional; compared PDR* cases with DR cases
Christiansen 1978	150 patients with insulin-dependent juvenile-onset diabetes of different durations	Cross-sectional
Wegener et al. 1980	674 Navajo Indians with diabetes mellitus	Cross-sectional
Gray et al. 1982	181 patients with type 1 diabetes with various levels of DR	Cross-sectional
Edwards et al. 1984	157 patients with insulin-dependent diagnosed at least 10 years ago; 118 seeking medical care and 116 with reliable non-diabetes	Cross-sectional
Delamaye et al. 1984	688 patients with insulin-dependent diabetes with a duration of 15–40 years	Cross-sectional
Rand et al. 1984	1,210 patients with insulin-treated diabetes with PDR and 1,210 controls without DR matched for duration of diabetes	Case-control; matched for duration of diabetes
Stolle 1985	672 equally treated patients with diabetes aged 20–29 years	Cross-sectional
Walker et al. 1985	155 diabetic patients	Cross-sectional
Barbano et al. 1986	Population-based cohort of 1,035 patients with adult-onset diabetes	Prospective for 10 years
Mills (Joslin Clinic) 1986	2,967 consecutive insulin-dependent diabetics	Retrospective review
[illegible] et al. 1986	184 survivors of long-term insulin-dependent diabetes participating in a prospective study	Cross-sectional
Kingsley et al. 1988	734 patients with insulin-dependent diabetes	Cross-sectional

*PDR = Proliferative diabetic retinopathy.
†NR = Data were not reported.
‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
§OR = Odds ratio.

Diabetes/DR assessment	Results
NR†	Smoking was associated with PDR in patients with a long duration of diabetes; there was no adjustment for [illegible] of control of diabetes
Standardized clinical progression of DR	Smoking was not associated with DR or PDR
Standardized clinical progression of DR	Smoking was not associated with DR or PDR
Standardized clinical examination	Patients with DR were more likely to be smokers, likely exposed to level of glycemic control; no dose-response pattern was noted
Fundus photographs graded according to the Airlie House classification	Data were not associated [illegible] pack-years and DR progression or DR
Clinical records, clinical examination, fundus photography, and fluorescein angiography	Smoking, including current and former smoking, were not associated with PDR
Standardized clinical examination, fundus photographs graded according to the Modified Airlie House classification	Smoking was [illegible] level, PDR
Standardized clinical examination for DR	There was an [illegible] relationship between DR and smoking; OR = [illegible] for current smokers
Standardized clinical examination	Smoking was [illegible] in men, but in Mexican-Americans, [illegible] for current and former smokers
Standardized DR by clinical examination	Smoking was not associated with incidence of DR or PDR
Standardized clinical examination by ophthalmologists	Smokers had a greater DR progression with [illegible] and [illegible] risk of PDR; [illegible] level of control of diabetes
Standardized clinical examination for DR graded in an unstandardized fashion	Smoking was associated with [illegible] for PDR
Standard examination by physician and angiography or otherwise self-reported	There were no univariate analyses or ranges for smokers with and without severe retinopathy; there were no adjustments for other factors

Table 6.29 Continued

Study	Population	Design
Moss et al. 1991	868 patients with early-onset and 1,378 with adult-onset diabetes	4-year prospective for incidence and progression of DR
Matsuda et al. 1993	277 patients with type 1 diabetes with [illegible] of 25 years	Prospective for 5 years; [illegible] 2–5 years
Klein et al. 1993	765 persons with younger-onset diabetes and cortical cataract; stage one: 4,926 and the [illegible] 5,924 [illegible] ambulatory [illegible] 10 years [illegible]	[illegible]
Moss et al. 1993	796 persons with early-onset and 491 with adult-onset diabetes	10-year prospective for progression of DR
Muhlhauser et al. 1996b	542 patients with type 1 diabetes	6-year [illegible] ros[illegible] for progression of DR
Sato et al. 1997	100 patients with [illegible] diabetes (Stage 4–5 excluded)	Prospective follow-up [illegible] years

*PDR = Proliferative diabetic retinopathy.

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Diabetes/DR assessment	Results
Fasting glucose/fundus photogr...h, graded according to modified Airlie syst...	Smoking was not associated with incidence or progression in either group with diabetes
...ted; DR by fundus photography, graded ...according to modified Airlie classification	Smoking was not associated with incidence of DR in either diabetic group
Fasting glucose/fundus ph...graphy, graded ...according to modified Airlie system	10-year cumulative incidence of diabetic macular edema was ... for current smoking history
Fasting glucose; fundus photography; genetic screening for diabetes; DR assessed	The ... eligible for and ... progression of ... was the incidence and ...
Self-report of diabetes; DR based on fundus exam and photography; ...ng system not described	Fund... were associated with any progression in retinal status from baseline status: OR = 1.44 (... years; 95% confidence interval, 1.10–1.88). There were no associations of smoking variables with incidence of DR or progression to PDR in the group without DR at baseline; adjusted for ...
NR	Smokers and non-DR at baseline had ... increased risk for development of ... levels of control of diabetes

Table 6.30 Studies on the association between smoking and glaucoma

Study	Population	Design	Glaucoma assessment	Results
Morgan and Drance 1975	Cases of glaucoma diagnosed by multiple ophthalmologists; neighborhood controls	Case-control	Data were not reported	Smoking was not related to glaucoma
Wilson et al. 1987	83 cases, 427 controls matched by age and gender	Case-control	Visual field exam, and eye ... examination; cases presumed open-angle; controls were found ...	...
Klein et al. 1993a	Population-based survey of 4926 adults aged 43 years and ...	Cross-sectional	Visual field exam, ... ophthalmic disc, and ... pressure; open-angle glaucoma ...	Smoking was not associated with open-angle glaucoma
Perkins et al. 1994	44 cases of glaucoma with ocular hypertension (intraocular pressure ≥21 mm Hg); 220 controls with intraocular pressure ≤21 mm Hg	Prospective (Cross-sectional)	Visual field and ... intraocular pressure	Smoking was not ... open-angle glaucoma
Quigley et al. 1994	617 persons with ocular hypertension followed for 7.2 years	Prospective	Intraocular pressure ... visual field exam ... annual visual field ... follow-up	Smoking was not ... ocular hypertension ... visual field loss
Tielsch et al. 1995	Population-based study of 4,314 Baltimore residents (302 glaucoma cases)	Cross-sectional	Visual field and optic disc ...	Smoking was not related ... glaucoma

Other Eye Diseases: Graves' Ophthalmopathy

Several other eye diseases have been investigated for an association with smoking. Most were not reviewed for this report, however, because the data are insufficient to reach any conclusions. The one exception is an uncommon condition—Graves' ophthalmopathy, an ocular complication of Graves' disease.

Graves' disease is thought to be an autoimmune disease of the thyroid. It is likely that both genetic and environmental factors are related to the risk of the disease. Among its clinical manifestations, the ophthalmologic complications appear to be related to smoking. Graves' ophthalmopathy is characterized by proptosis (protrusion of the eyeball), diplopia (double vision), optic neuropathy, and conjunctival and periorbital inflammation. The pathogenesis of Graves' ophthalmopathy is not completely understood, but it appears to involve the orbital fibroblasts that are stimulated to release glycosaminoglycans, which in turn are related to the orbital edema seen with the ocular complications. Recent data suggest an autoimmune basis for Graves' ophthalmopathy as well (Rahn 2000).

Biologic Basis

The mechanism by which smoking may cause or aggravate Graves' ophthalmopathy is unknown. Orbital hypoxia and effects of thiocyanate have been postulated, and other research has investigated the effect of smoke constituents on orbital fibroblast activity. Researchers investigating the role of hypoxia in muscular inflammation have found stimulation of protein synthesis and proliferation of extra-ocular, muscle-derived fibroblasts under hypoxic conditions (Metcalfe and Weetman 1994). Smoking does not appear to affect serum concentrations of proinflammatory cytokines in Graves' disease, even among persons with ocular complications (Salvi et al. 2000).

Epidemiologic Evidence

Seven studies (Table 6.31) found an increased risk associated with smoking of developing the ophthalmologic complications of Graves' disease (Hägg and Asplund 1987; Shine et al. 1990; Tellez et al. 1992; Prummel and Wiersinga 1993; Winsa et al. 1993; Pfeilschifter and Ziegler 1996; Bartalena et al. 1998); three found a dose-response relationship with the number of cigarettes smoked (Shine et al. 1990; Tellez et al. 1992; Pfeilschifter and Ziegler 1996). The studies, while consistent, are limited in number and the sample sizes of some are small. The severity of the ophthalmopathy was associated with smoking in two studies (Prummel and Wiersinga 1993; Winsa et al. 1993). Estimates of the OR varied between 2 and 10, depending on the control population selected. The effect of quitting smoking on Graves' ophthalmopathy has not been well studied and would provide convincing evidence of a causal relationship. On the basis of the findings of the epidemiologic studies, several investigators are studying the effect of smoking on the thyroid gland and the extra-ocular, muscle-derived fibroblasts.

Evidence Synthesis

Although there are suggestive epidemiologic findings, the biologic basis for a role of smoking in Graves' ophthalmopathy is unclear. The epidemiologic data are still limited, although consistent in indicating an increased risk in smokers. Dose-response is not well documented.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Implication

Data on the role of smoking cessation in preventing or lessening the severity of the ophthalmopathy would be important to understanding the relationship between Graves' disease and smoking.

Table 6.31 Studies on the association between smoking and Graves' ophthalmopathy

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Hägg and Aspland 1987	12 persons with Graves' ophthalmopathy, 24 controls with Graves' disease and no ophthalmopathy, 48 population controls	Case-control	Clinical exam	Smoking increased the OR* of ophthalmopathy compared with no ophthalmopathy among persons with Graves' disease. OR = 10.0 (95% C.I. 1.4–74.9), and with population controls, OR = 20.2 (...
Shine et al. 1990	85 persons with ophthalmopathy, 62 with Graves' disease, 81 controls without Graves' disease	Case-control	Clinical exam	Tobacco history, likely to be smokers ... years; dose-response ... (p<0.05)
Tellez et al. 1992	166 patients with newly diagnosed Graves' disease	Cross-sectional	Clinical exam using American Thyroid Association Classification system	... positive pressure was higher in smokers and in former smokers (... 7.4 (95% C.I. 1.1–51); there was a dose-response pattern with cigarette-years†
Prummel and Wiersinga 1993	160 treated Graves' ophthalmopathy, 160 cases of Graves' disease without ophthalmopathy, 175 general population controls, 75 cases of hyperthyroidism, 47 controls	Case-control	Clinical exam	Graves' ophthalmopathy cases and ... cases ... ...

Table 6.31 Continued

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Pfeilschifter and Ziegler 1996	253 patients with recent onset of Graves' disease	≥1 year prospective	Clinical exam/ patient report of double vision (diplopia) and exophthalmometer readings >20 mm (proptosis)	Current smoking was associated with incidence of symptomatic ophthalmopathy. OR = 1.2 (95% CI, 1.1–1.6) proptosis. OR = 2.6 (95% CI, 1.8–3.9), and diplopia, OR = 3.1 (95% CI, 1.7–6.0); there was a dose-response relationship; former smokers [illegible] no increased risk
Bartalena et al. 1999	480 patients with mild ophthalmopathy [illegible] 6 of 7 centers; 76 patients with severe ophthalmopathy [illegible]	Prospective [illegible] progression	Clinical grading by 3 ophthalmologists assessing the clinical activity score modified to [illegible]	Multivariate analysis was more likely to progress to [illegible] with current smoking [illegible] [illegible] [illegible]

Peptic Ulcer Disease

In the early 1990s, the central role played by the bacterium *Helicobacter pylori* (*H. pylori*) in both the incidence and recurrence of peptic ulcer disease was recognized (Kuipers et al. 1995). This section reviews the evidence of an association between smoking and peptic ulcer disease in light of this new understanding of the pathogenesis of ulcer disease. Relevant articles were identified through a MEDLINE search from 1985 through June 2000 using the following terms: "ulcer and smoking and pylori" and "smoking and pylori and eradication." A further search was performed for the years 1998 through June 2000, using the terms "ulcer and smoking" to identify any major studies that were not included in the previous Surgeon General's report (USDHHS 2001), even though the studies had not evaluated *H. pylori*.

Conclusions of Previous Surgeon General's Reports

Numerous studies have demonstrated an association between smoking and the occurrence of peptic ulcer disease. This evidence was reviewed in the 1964, 1971, and 1972 Surgeon General's reports on smoking and health (USDHEW 1964, 1971, 1972). The 1979 report concluded that cigarette smoking was significantly associated with both the incidence and an increased risk of dying from peptic ulcer disease. "the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship" (USDHEW 1979, p. 1-23). In addition, that report concluded that there was highly suggestive evidence that smoking also retards ulcer healing. The 1990 report concluded that smokers had an increased risk of developing both duodenal and gastric ulcers, and smoking cessation reduced that risk (USDHHS 1990). That report also found that among smokers ulcer disease was more severe, duodenal ulcers were less likely to heal, and both duodenal and gastric ulcers were more likely to recur. Ulcer patients who stopped smoking, however, were found to have an improved clinical course compared with continuing smokers. Although much of this previous evidence was based largely on studies of men, the more recent Surgeon General's report on women and smoking (USDHHS 2001) concluded that women who smoked also had an increased risk of peptic ulcer disease.

Biologic Basis

In the decades since the 1964 Surgeon General's report, explanations of the pathogenesis of peptic ulcer disease have changed dramatically with the identification of the gastric bacterium *H. pylori* in a high proportion of patients with peptic ulcers (Marshall and Warren 1984). Up to 100 percent of duodenal ulcers and 70 to 90 percent of gastric ulcers are now associated with *H. pylori* infection (Kuipers et al. 1995). Most ulcers in persons without *H. pylori* infection were linked to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Borody et al. 1991, 1992a). Other causes of peptic ulcers, although rarer, include Crohn's disease and Zollinger-Ellison syndrome.

Normally, the gastrointestinal mucosa is protected from injury by, among other factors, a layer of mucus and the secretion of bicarbonate by [illegible] and duodenal epithelial cells to neutralize [illegible]. If these protective mechanisms are [illegible] or there is an increase in levels of damaging [illegible], then ulceration may occur.

Effects of Smoking on Gastrointestinal Physiology

The 1990 Surgeon General's report (USDHHS 1990) reviewed the effects of cigarette smoking on aspects of human gastrointestinal physiology relevant to peptic ulcer disease. Likely mechanisms whereby smoking could promote the development of peptic ulcer disease included the potential for tobacco smoke and/or nicotine to increase maximal gastric acid output and duodenogastric reflux and to decrease alkaline pancreatic secretion and prostaglandin synthesis.

Two subsequent reviews (Endish and Leung 1994; Eastwood 1997) evaluating the potential effects of cigarette smoke and nicotine as injurious and protective factors that could play a role in peptic ulcer formation came to similar conclusions. Data on the effects of smoking on gastric acid secretion in humans have been highly inconsistent; multiple reports found that smoking and/or nicotine variously stimulated, inhibited, or had no effect on gastric acid secretion. However, there was more consistent evidence that smoking promotes reflux of duodenal contents into the stomach, and increases production of free radicals and the release of vasopressin, a potent vasoconstrictor. Protective mechanisms consistently affected by smoking were the chronic inhibition of gastric mucus secretion,

cytoprotective prostaglandin production, pancreatic and duodenal mucosal bicarbonate secretion, and a decrease in mucosal blood flow.

The mucosal protection mechanism most clearly affected by smoking is the pancreatic secretion of bicarbonate. A transient reduction in secretion is seen immediately after smoking, leading to a drop in pH in the duodenal bulb (Eastwood 1997). Acidity in the duodenal bulb appears to be the most important determinant for the development of gastric metaplasia in the duodenum, thus paving the way for duodenal colonization by *H. pylori* (Tytgat et al. 1993).

Results from studies evaluating mucosal blood flow among smokers and nonsmokers have been more varied, possibly because of a variation in the measurement methods. Taha and colleagues (1993) demonstrated that both gastric and duodenal mucosal blood flow were reduced in chronic NSAID users. However, after allowing for NSAID use, significantly reduced duodenal blood flow was seen only in *H. pylori*-positive smokers. There was an additional effect of either *H. pylori* infection or smoking on gastric mucosal blood flow.

Finally, some strains of *H. pylori* produce a vacuolating toxin that may be important in determining the virulence of the organism. This toxin induces vacuolation of HeLa cells in vitro, as does nicotine alone, but the addition of nicotine to *H. pylori* potentiates the vacuolating effect of the toxin (Cover et al. 1992).

In summary, studies document that smoking appears to have a multitude of effects on gastroduodenal physiology, and through a number of mechanisms, it could promote peptic ulceration. These effects are, however, largely transient, and the affected physiologic measures return to normal within minutes or hours after smoking cessation (Eastwood 1997). These same studies also indicate that smoking could particularly increase the likelihood of ulceration in *H. pylori*-positive persons.

Smoking and *Helicobacter pylori* Infection

Both *H. pylori* infection (Malaty et al. 1992; EUROGAST Study Group 1993) and smoking (Bergen and Caporaso 1999) are more common among groups of lower SES. Cross-sectional studies that have evaluated the association between *H. pylori* infection and smoking in healthy volunteers consistently have reported higher infection rates in smokers (current or former) than in nonsmokers. In a study of 485 volunteers in the United States, current and former smokers were more likely to be seropositive for *H pylori* than nonsmokers (among blacks, rates were 73 percent among current smokers, 85 percent among former smokers, and 61 percent among nonsmokers; and among whites, rates were 40 percent, 48 percent, and 25 percent, respectively) (Graham et al. 1991). Infection also was slightly more common among 3,496 adult smokers in Northern Ireland (65 percent among former smokers, 57 percent among smokers of fewer than 20 cigarettes, and 64 percent among smokers of 20 or more cigarettes per day compared with 53 percent among people who had never smoked) (Murray et al. 1997). Similar findings were seen in a group of 273 adults from Melbourne, Australia, among current and former smokers (45 percent and 44 percent, respectively, compared with 31 percent in people who had never smoked) (Lin et al. 1998) and among 1,064 adult heavy smokers in New Zealand (38 percent in smokers of more than 20 cigarettes per day compared with 23 percent in smokers of less than 20 cigarettes per day and nonsmokers) (Collen et al. 1999). Similar patterns have been reported in adults visiting general practitioners in Germany (Brenner et al. 1997) and in patients undergoing an endoscopic examination in the United Kingdom (Bateson 1998) and Malaysia (Goh 1997).

In some of these studies, the association between *H. pylori* and smoking was attenuated after adjusting for other factors, including age and SES. In both developed and developing countries, *H. pylori* infection is believed to occur during childhood (Xia and Talley 1997), and thus it is unlikely that smoking influences the risk of initial *H. pylori* infection to any great extent. It is unclear whether smoking could be a risk factor for the acquisition or persistence of *H. pylori* infection in adulthood or if low SES is a common, more distal risk factor for both *H. pylori* and smoking. These variables do not, however, alter the fact that smokers are more likely than nonsmokers to be infected with *H. pylori*. The link between *H. pylori* and peptic ulcer disease is well established; thus, it is important to consider whether smoking also is a risk factor or if some or all of the observed associations between smoking and peptic ulcer disease could be due to confounding by *H. pylori* infection status.

Trends in Peptic Ulcer Disease

During the past several decades, rates of hospitalization for and mortality from peptic ulcer disease in the United States have declined dramatically. Using hospitalization rates from the computerized database of the U.S. Department of Veterans Affairs, El-Serag and Sonnenberg (1998) showed that although gastric ulcers accounted for 67.6 and duodenal ulcers

for 188.8 out of every 10,000 hospitalizations of veterans from 1970–1974, comparable figures for 1990–1995 were 49.6 per 10,000 and 52.5 per 10,000, respectively. Similarly, using vital statistics data from CDC's National Center for Health Statistics, these two authors showed that mortality from gastric ulcer disease had fallen from 17.4 per million per year in 1968–1972 to 7.7 per million per year in 1988–1992, with a comparable drop in mortality for duodenal ulcer disease from 19.6 to 8.4 per million per year (El-Serag and Sonnenberg 1998). However, peptic ulcer disease still is a leading cause of morbidity. In 1989, the National Health Interview Survey included a special questionnaire on digestive diseases. Among approximately 42,000 adult respondents, 10 percent reported that they had ever had a physician-diagnosed peptic ulcer, one-third of whom also reported having a new or recurring ulcer in the past 12 months (Sonnenberg and Everhart 1996). Among the 50 percent who reported the site of their ulcer, gastric and duodenal ulcers were equally common overall, although nonwhites reported gastric ulcers more frequently and duodenal ulcers less frequently than whites. When recurrent ulcers, defined as a relapse in the past 12 months of a previously diagnosed ulcer, were excluded, the incidence of new peptic ulcers in 1989 was an estimated 52.7 per 10,000 (Everhart et al. 1998). Among those respondents who specified the site of the ulcer, the incidence of gastric ulcers (17.0 per 10,000) was about three times that of duodenal ulcers (6.1 per 10,000). This finding suggests that the incidence of new duodenal ulcers may have fallen more rapidly over time than that of gastric ulcers.

A large part of the decrease in peptic ulcer rates over the last few decades in the United States has been attributed to lower smoking rates (Kurata et al. 1986), although the same pattern was not seen in the United Kingdom (Sonnenberg 1986). However, the prevalence of *H. pylori* infection in developed countries also is believed to have declined over a similar time period (Banatvala et al. 1993; Kosunen et al. 1997), and it is this decline, rather than falling smoking rates, that may explain some or all of the reductions in ulcer rates.

Epidemiologic Evidence

Smoking and Development of Peptic Ulcer

Studies that evaluated the relationship between tobacco smoking and the development of peptic ulcer disease repeatedly have shown an increased risk of both duodenal and gastric ulcers among smokers (USDHEW 1979; USDHHS 1990). In some studies, this risk also has been observed to increase with increasing levels of smoking. During a 149,291 person-years follow-up of a cohort of 7,624 Japanese men in Hawaii, the age-adjusted incidence of gastric and duodenal ulcers increased with increasing levels of smoking at baseline (RR among nonsmokers and smokers of less than 24, 24 through 40, and greater than 40 pack-years: 1.0, 1.5, 3.1, and 3.8 [P_{trend} <0.01], respectively, for gastric ulcers and 1.0, 1.8, 2.4, and 3.3 [P_{trend} <0.01], respectively, for duodenal ulcers [Jiang et al. 1992]). In contrast, an analysis of self-reported ulcer history, using data from the 1989 National Health Interview Survey in the United States, suggested that smoking may be a stronger risk factor for chronic ulceration than for the development of new ulcers (Everhart et al. 1998). Although these data show a strong relation between smoking and age-standardized prevalence of chronic active ulcers (1.8 percent, 5.0 percent, 3.9 percent, and 5.3 percent among nonsmokers and smokers of <20, 20, and >20 cigarettes per day, respectively), there was no association between smoking and the incidence of new ulcers.

Helicobacter pylori, Smoking, and Peptic Ulcer

Only a few studies have considered both smoking and *H. pylori* infection in relation to the incidence of peptic ulcer disease (Table 6.32). These studies largely have been cross-sectional surveys of patients referred for upper gastrointestinal endoscopy using variable definitions of smoking, and rarely presenting results that distinguished between smokers with and without *H. pylori* infection. No studies have separately evaluated the risk of peptic ulcers in former smokers after allowing for *H. pylori* infection.

Four of these studies were conducted with groups receiving endoscopic examinations. Martin and colleagues (1989) found no duodenal ulcers in 47 *H. pylori*-negative persons although 4 of them, all of whom were taking NSAIDs, had a gastric ulcer. Among the 60 *H. pylori*-positive persons, peptic ulcers were significantly more common in smokers than in nonsmokers. Similarly, Talamini and colleagues (1997) reported a significant association between duodenal ulcers and smoking after adjusting for *H. pylori* infection. In a Swiss study, smoking also appeared to be associated with an increased risk of duodenal ulcers, particularly among *H. pylori*-positive persons (Halter and Brignoli 1989). The lack of a single reference group in this study, however, makes comparisons with other studies difficult. In contrast, Schubert and colleagues (1993) reported no significant differences between the

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proportion of smokers in patients with and without ulcers and, as a consequence, did not include smoking status in their multivariable models adjusting for *H. pylori*. It is possible, however, that the very broad definition of smoking used in this last study may have led to very light or occasional smokers being inappropriately classified as smokers, thus masking differences between patients with and without ulcers.

Two other studies used groups of company employees. Wang and colleagues (1996) conducted a case-control study in a factory in Shanghai, China. To prevent confounding by SES and gender, data were analyzed separately for men and women, drivers and workers (lower SES), and staff (higher SES). Among male workers and drivers (304 cases and 263 controls), current smoking was associated with a significantly elevated risk of peptic ulcer disease that increased with the amount of cigarettes smoked. A similar pattern was seen for duodenal ulcer disease alone. There was only one female employee smoker, and too few former smokers to evaluate risks in those groups. Although smoking status was assessed after the development of ulcers, smoking rates were high and few workers reported having stopped smoking. It is therefore unlikely that many employees changed their smoking behavior following ulcer diagnosis.

Schrieiper and colleagues (1996) conducted parallel studies in companies in Japan and the Netherlands. Men and women with verifiable ulcer disease who had not been treated with *H. pylori* eradication therapy were compared with those without ulcers or prior gastric surgery. After adjusting for potential confounders, researchers found that daily smoking was associated with a nonsignificant increased risk of peptic ulcer disease only in the Dutch population. In this study, the majority of ulcers had been diagnosed a median of six years before smoking data were collected, and it is possible that employees with peptic ulcer disease may have changed their smoking behaviors over time.

There is a potential for bias in any of these studies if participants altered their smoking behaviors because of ulcer symptoms or if they misreported their smoking patterns. If ulcer patients tend to stop or reduce their smoking because of symptoms, or if they systematically underreport the amount they smoke, then the true associations between smoking and ulcers could be greater than those reported. Conversely, if ulcer patients actually increase their smoking in response to ulcer symptoms or if they systematically overreport the amount they smoke, then the observed associations could exaggerate the true effect. This latter situation would seem less likely than the former.

Nonsteroidal Anti-Inflammatory Drugs, Smoking, and Peptic Ulcer

The main cause of ulcers in persons negative for *H. pylori* infection, at least in developed countries, is the use of NSAIDs (Baroody et al. 1991, 1992a). In the 1990 Surgeon General's report (USDHHS 1990), smoking was associated with peptic ulcer disease and acute gastric erosions in three studies of NSAID users. Since then, three more studies have evaluated the relationship between smoking and peptic ulcers in NSAID users, with conflicting results.

Hansen and colleagues (1996) compared 94 NSAID users admitted to a hospital with complications of peptic ulcers (predominantly bleeding or perforated ulcers) with 324 controls selected at random from all assumed NSAID users. Overall, cases were no more likely than controls to be smokers (44 percent and 41 percent, respectively), but after adjusting for age, gender, ulcer history, and duration of NSAID use, current smoking was associated with an almost twofold increased risk of ulcer complications (OR = 1.9 [95 percent CI, 1.0–3.6]).

In contrast, Aalykke and colleagues (1999) compared 132 current NSAID users diagnosed with bleeding peptic ulcers with 136 ulcer-free NSAID users selected from a rheumatology clinic and geriatrics department. Smokers were not at an increased risk of developing bleeding ulcers compared with controls (OR, adjusted for age, gender, ulcer history, *H. pylori* infection status, and NSAID dose = 0.91 [95 percent CI, 0.48–1.71]). Similarly, in a large case-control study in the United Kingdom, Weil and colleagues (2000) compared 1,121 patients diagnosed with bleeding peptic ulcers with 989 community controls. Information on *H. pylori* infection status was not available, but among NSAID users the risk for bleeding peptic ulcers (compared with nonsmokers who did not use NSAIDs) did not differ appreciably between current smokers (OR = 4.0 [95 percent CI, 2.9–5.5]) and nonsmokers (OR = 3.6 [95 percent CI, 2.9–4.5]).

Mortality from Peptic Ulcer

Large-scale cohort studies consistently have shown that smokers are at a greater risk of dying from peptic ulcer disease than nonsmokers (USDHHS 1990). Follow-up of the U.S. Veterans Study now has been extended to 26 years, with a total of 5.4 million person-years. Smoking information was collected only at baseline. To allow for the fact that many current smokers at baseline subsequently would have stopped smoking, the analysis was restricted to people who never smoked (who were unlikely to have started

Table 6.32 Studies on the association between smoking and peptic ulcer disease, allowing for *Helicobacter pylori* (*H. pylori*) infection

Study/location	Population	Definition of smoking
Martin et al. 1989 United States	107 patients referred for endoscopy, including 14 with duodenal ulcers, 14 with gastric ulcers, and 19 healthy volunteers	>10 cigarettes/day
Schrieiper et al. 1996 Japan and the Netherlands	1,033 patients referred for endoscopy, including 297 with duodenal ulcer, 97 with gastric ulcer, and 5 with both duodenal and gastric ulcers	At least 1 cigarette/day for 1 year before examination
Schrieiper et al. 1996 Japan and the Netherlands	214 Japanese and 193 Dutch couples each with a patient with peptic ulcer disease (including 63 with active peptic ulcers, including 16 cases since diagnosis, and 5 with active duodenal ulcer)	Current (at least 1 cigarette/day) smoker
Wang et al. 1996 China	Factory employees: 304 cases (with any peptic ulcer within previous 2 years and 1,959 cases (duodenal ulcer) in survey	Current (at least 1 cigarette/day) smokers included
Talamini et al. 1997 Italy	555 patients referred for endoscopy, including 54 with duodenal ulcers and 24 with gastric ulcers	Daily cigarette smoking
Hellers and Bolgovi 1998 Switzerland	283 patients referred for endoscopy, including 24 with duodenal ulcers and 9 with gastric ulcers	Daily cigarette smoking

[a]OR = Odds ratio.
[b]CI = Confidence interval.

Results

Prevalence of peptic ulcers among *H. pylori*-positive patients:
Smokers
Nonsmokers

was found between smoking and peptic ulcer prevalence in [illegible]

OR

Smokers vs. nonsmokers

OR

	Ulcer cases	Controls
Any peptic ulcer		
1–19 cigarettes/day		
≥20 cigarettes/day		
Duodenal ulcer		
1–19 cigarettes/day		
≥20 cigarettes/day		

Patients with duodenal ulcers (smokers [illegible] cigarettes/day, 95 percent CI, [illegible]; >20 cigarettes/day, 2.0 [illegible])

Odds ratio for duodenal ulcer, smokers vs. nonsmokers:

Duodenal ulcer, total (including [illegible] percent)	
[illegible]	
[illegible]	

Crude OR (95 percent CI) for each group vs. other 2 groups combined

Duodenal ulcer vs. controls by [illegible] group	
[illegible] negative nonsmokers	0.13 (0.02–0.97)
[illegible] negative smokers	0.27 (not reported)
[illegible] positive nonsmokers	0.89 (not reported)
[illegible] positive smokers	9.55 (1.90–15.61)

smoking) and to former smokers at baseline. Former smokers had elevated risks for mortality from both duodenal ulcer disease (OR = 1.8 [95 percent CI, 1.3–2.4]) and gastric ulcer disease (1.6 [1.1–2.2]) (NIH 1997). During follow-up of the British doctors cohort, information about smoking behaviors was collected at baseline in 1951 and again in 1957, 1966, 1972, 1978, and 1990. After 40 years, mortality from peptic ulcer disease was 8 per 100,000 per year among men who had never smoked cigarettes; 12 per 100,000 per year among former smokers; and 11, 33, and 34 per 100,000 per year among current smokers of 1 to 14, 15 to 24, and 25 or more cigarettes per day, respectively (p <0.001) (Doll et al. 1994). None of these studies, however, could explore possible confounding of this association by *H. pylori* infection.

Effect of Smoking on Ulcer Severity

Ulcers may be more severe and complications may occur more frequently among continuing smokers (USDHHS 1990). Hasebe and colleagues (1998) compared 35 patients with deep gastric ulcers (ulceration beyond the muscularis propria) and 33 patients with shallow and intermediate depth ulcers (ulceration in submucosa and muscularis propria) in Japan. They found that patients with deep ulcers were more likely to be heavy smokers, defined as smoking 20 or more cigarettes per day, than patients with shallower ulcers (81 percent versus 55 percent, p <0.05). However, patients with deep ulcers also were significantly more likely to drink alcohol on a daily basis (40 percent versus 21 percent, p <0.05) and to have *H. pylori* infections (97 percent versus 79 percent, p <0.01), so it is possible that these differences could explain some or all of the associations with smoking.

Smoking and Peptic Ulcer Complications

Svanes and colleagues (1997) compared patients diagnosed with perforated peptic ulcers with population controls (99 percent response rate) in Norway. Analyses of smoking were restricted to cases (36 gastric perforation and 73 duodenal perforation) and controls (n = 4,270) aged 15 through 74 years because smoking was rare in older patients. After adjusting for age and gender, the risk of perforated ulcers in current smokers increased significantly with the number of cigarettes smoked per day. The ORs were 7.3 (95 percent CI, 4.0–16.1) for smokers of 1 to 9 cigarettes per day, 8.7 (95 percent CI, 3.5–14.4) for smokers of 10 to 19 cigarettes per day, and 11.2 (95 percent CI, 6.3–27.5) for smokers of 20 or more cigarettes per day (p <0.001) compared with people who had never smoked. The risk among former smokers was no greater than that among those who had never smoked (OR = 0.8 [95 percent CI, 0.2–2.2]). Smokers were less likely than nonsmokers to have used NSAIDs or other ulcerogenic drugs. Thus, variation in NSAID use could not explain the relationship with smoking. The high alcohol consumption, however, which was significantly more common among current smokers (25 percent versus 4 percent among nonsmokers), could possibly explain some of the strong associations between smoking and perforated ulcers. *H. pylori* infection was not assessed, but among the cases, 87 percent of smokers and 96 percent of nonsmokers reported previous "ulcer dyspepsia," suggesting that infection rates probably were high in both groups.

Lanas and colleagues (1997) conducted a similar study in Spain, comparing 76 patients with gastrointestinal perforation (including 31 with duodenal ulcers and 28 with gastric ulcers) with matched hospital and community controls. After adjusting for the use of NSAIDs and alcohol and histories of ulcers and arthritis, smoking was again associated with a significantly increased risk of perforated ulcers (p = 0.003). In Italy, Labenz and colleagues (1998) compared 72 patients admitted with bleeding peptic ulcers with matched hospital controls. After adjusting for *H. pylori* infection status, NSAID use, and alcohol intake, smoking was associated with a nonsignificant 40 percent increased risk of bleeding ulcers (OR = 1.4 [95 percent CI, 0.5–3.8]).

In the large case-control study conducted by Weil and colleagues (2000) in the United Kingdom, overall current smoking was associated with a 60 percent increased risk of bleeding peptic ulcers (OR = 1.6 [95 percent CI, 1.2–2.0]). This risk appeared to differ, however, between users and nonusers of NSAIDs. Among NSAID nonusers, smoking was associated with an almost twofold increased risk of bleeding ulcers (OR = 1.9 [95 percent CI, 1.4–2.4]). In contrast, the risk for peptic ulcers in NSAID users did not differ appreciably between current and nonsmokers as described above.

Effect of Smoking on Ulcer Healing and Recurrence

Ulcer Healing

Many studies have shown that smoking adversely affects healing of duodenal ulcers by acid-reducing agents (Lanas 1990, USDHHS 1990). It does not appear, however, to have the same adverse effect

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on healing by other agents, including sucralfate (Lam 1991) or colloidal bismuth subcitrate (Lam 1991; Lambert 1991). In a meta-analysis, data from six studies of sucralfate were combined, giving overall healing rates of 78 percent among 301 smokers and 78 percent among 272 nonsmokers (Lam 1991). In the same analysis, data also were pooled from three studies of colloidal bismuth subcitrate, giving healing rates of 82 percent among 93 smokers and 78 percent among 38 nonsmokers. Less consistent results were reported for the effects of smoking on gastric ulcer healing, although studies evaluating the benefits of smoking cessation have suggested that ulcer patients who stop smoking do better than patients who continue to smoke (USDHHS 1990).

Rates of ulcer healing are significantly higher (Hentschel et al. 1993; Lahenz and Börsch 1994) and recurrence rates significantly lower (Rauws and Tytgat 1995) among patients with ulcers (gastric or duodenal) who received *H. pylori* eradication therapy, which now is the recommended treatment for patients with *H. pylori* infection (NIH 1997). The combined effects of smoking and *H. pylori* eradication on ulcer healing in the short term have not been directly evaluated; however, in three studies of ulcer patients treated with *H. pylori* eradication therapy, there were no significant differences in ulcer healing rates between smokers and nonsmokers (O'Connor et al. 1995; Bardhan et al. 1997; Kadayifci and Simsek 1997). O'Connor and colleagues (1995) reported healing rates for gastric and duodenal ulcers of 83 percent for smokers compared with 92 percent for nonsmokers ($p = 0.3$), the *H. pylori* eradication rate also was slightly lower among smokers (83 percent versus 94 percent, $p = 0.2$), possibly explaining the slightly different healing rates. Bardhan and colleagues (1997) reported duodenal ulcer healing in 96 percent of smokers compared with 94 percent of nonsmokers ($p = 0.6$), whereas rates of *H. pylori* eradication were slightly higher for nonsmokers (77 percent versus 71 percent, $p = 0.5$). Kadayifci and Simsek (1997) reported duodenal ulcer healing in 82 percent and 83 percent of heavy (more than 20 cigarettes per day) and mild (1 to 20 cigarettes per day) smokers, respectively, compared with 85 percent of nonsmokers ($p = 0.9$). In this study, *H. pylori* eradication rates were slightly higher for nonsmokers (68 percent versus 56 percent among mild and 59 percent among heavy smokers). These reports suggest that ulcer healing rates are high in patients treated with *H. pylori* eradication therapy, regardless of their smoking status.

Duodenal Ulcer Recurrence

In studies comparing duodenal ulcer recurrence rates for smokers and nonsmokers before the introduction of *H. pylori* eradication therapy, higher relapse rates consistently were reported for smokers (USDHHS 1990). However, ulcers rarely, if ever, recur in patients who remain free of *H. pylori*, regardless of their smoking status. George and colleagues (1990) observed no recurrence of duodenal ulcers among 71 patients (31 current and 12 former smokers, and 28 lifetime nonsmokers) whose ulcers had healed, whose *H. pylori* had been eradicated, and who remained free of *H. pylori* during the four years they were followed. In an Australian study, 197 patients successfully treated for *H. pylori*-positive duodenal ulcers had their infections eradicated and their ulcers cured. They then were followed for 12 to 73 months (Borody et al. 1992b). There was no recurrence of *H. pylori* or duodenal ulcers among the groups of 80 current smokers (smoking 5 to 40 cigarettes per day), 38 former smokers (who gave up smoking during follow-up or up to 20 years earlier), and 79 patients who had never smoked. In the Netherlands, Van Der Hulst and colleagues (1997) also found no recurrences in 141 duodenal ulcer patients whose ulcers had been cured and who had been treated successfully for *H. pylori* infection; they remained free of infection during nine years of follow-up. In Greece, there was no recurrence of duodenal ulcers during 12 to 72 months of follow-up in 141 patients who remained *H. pylori* negative, regardless of their smoking status; there were seven recurrences (six in smokers) among 24 patients (unknown number of smokers) who became reinfected with *H. pylori* (Archimandritis et al. 1999).

Although other authors have documented low ulcer recurrence rates in patients whose *H. pylori* infection was eradicated, ulcer recurrence commonly is associated with either reinfection with *H. pylori* (Bayerdörffer et al. 1993) or NSAID use (Chen et al. 1996). Furthermore, recurrence rates have not varied between smokers and nonsmokers. A study in Hong Kong followed patients for 10 to 18 months who had been successfully treated for *H. pylori* infection and whose duodenal ulcers had healed (Chan et al. 1997). The authors documented two recurrences (2.9 percent, both *H. pylori* negative) among 68 smokers (≥10 cigarettes per day) and four recurrences (2.1 percent, three *H. pylori* negative) among 188 persons who had never smoked or were former smokers. The study concluded that smoking did not influence ulcer recurrence after *H. pylori* eradication.

Patients treated for *H. pylori*-positive duodenal ulcers in a multicenter study (Canada, Ireland, United Kingdom, and United States) were followed for six months (Bardhan et al. 1997). All patients had healed ulcers, but *H. pylori* was eradicated in only 77 percent of nonsmokers and 71 percent of smokers. Ulcers recurred in 22 percent of 118 smokers and 16 percent of 117 nonsmokers ($p = 0.32$). The slightly higher rate seen in smokers could be a result of the slightly lower *H. pylori* eradication rate for this group. Recurrence rates in this study among patients who apparently remained free of *H. pylori* during follow-up were an unusually high 12 percent (<6 percent in three of the centers) for both smokers and nonsmokers.

In summary, smoking does not appear to affect duodenal ulcer recurrence rates in patients whose *H. pylori* infection has been eradicated. Among those who remain *H. pylori* positive, smoking may increase the risk of relapse, although no good data support or refute this possible association.

Gastric Ulcer Recurrence

A similar pattern is seen for *H. pylori*-positive gastric ulcers, which also rarely recur after successful *H. pylori* eradication therapy in the absence of NSAID use (Lahenz and Börsch 1994). There were no relapses of gastric ulcers in 45 patients who remained *H. pylori* negative during 10 years of follow-up (Van Der Hulst et al. 1997). Chan and colleagues (1997) observed one recurrence of gastric ulcer accompanied by the reappearance of *H. pylori* in 15 smokers and no recurrences in 16 nonsmokers followed for up to 18 months after *H. pylori* eradication and successful ulcer healing.

These data suggest that for both gastric and duodenal ulcers, the main predictor of successful ulcer healing with no recurrence is *H. pylori* infection status. If smoking has any effect on the healing or recurrence of ulcers, it is therefore likely to be through an effect on the process of *H. pylori* eradication.

Smoking and Helicobacter pylori Eradication

A number of studies have evaluated the effects of smoking on *H. pylori* eradication. Results of studies that included more than 50 participants and presented separate eradication rates for smokers and nonsmokers are shown in Table 6.33. (Because three other studies [Fraser et al. 1996; Harris et al. 1996; Georgopoulos et al. 2000] simply reported that smoking was not significantly associated with eradication without presenting eradication rates, it is not possible to tell if there were nonsignificant differences between smokers and nonsmokers.) Although the definition of smoking in these studies often is unclear, and a range of different drug combinations was used to treat the infections, a fairly consistent pattern of lower eradication rates is seen in groups defined as smokers.

Other factors known to be strongly predictive of *H. pylori* eradication are compliance with therapy (Graham et al. 1992; Cutler and Schubert 1993; Labenz et al. 1994) and the prevalence of metronidazole resistance (O'Riordan et al. 1990). Although some studies have reported no [illegible] compliance among smokers (Unge et [illegible] have found similarly high compliance [illegible] smokers and nonsmokers (Connor [illegible] Bardhan et al. 1997; Karnada et [illegible] 1999). In a [illegible] regression model also adjusting for therapy duration and omeprazole pretreatment, Labenz and colleagues (1994) found both lack of compliance (OR = 74.72 [95% CI, 24.17–205.51]) and smoking (OR = 2.75 [95% CI, 1.56–4.86]) to be independent risk factors for treatment failure. Wittenburg and colleagues (1993) found that metronidazole resistance developed more readily in smokers following therapy with bismuth and metronidazole after allowing for variations in compliance ($p = 0.01$). However, poorer eradication rates in smokers also are seen with regimens that do not contain this class of drug. Therefore, it seems unlikely that the lower eradication rates for smokers can be attributed to either poorer compliance or an increase in metronidazole resistance. It has been suggested that smoking may adversely affect eradication by increasing acid output or by decreasing gastric blood flow, thereby reducing drug delivery to the gastric mucosa, but little evidence supports either of these hypotheses.

Evidence Synthesis

Incidence of Peptic Ulcer

Many studies have reported strong and significant associations between smoking and peptic ulcer disease. Only six studies, however, have allowed for the effects of *H. pylori* infection when evaluating this association. Three of those studies reported significantly increased risks of ulcer disease in smokers after adjusting for *H. pylori* infection; in each study, the majority (80 to 90 percent) of ulcer patients were *H. pylori* positive (Wang et al. 1996; Talamini et al. 1997; Halter and Brignoli 1998). A fourth study reported a significant association between smoking and ulcers

only among *H. pylori*-positive persons (Marilu et al. 1999). The remaining two studies (Schubert et al. 1993; Schlemper et al. 1998) reported little or no association, but the classification of smoking status in these studies is potentially unreliable.

Cigarette smoking has a number of effects on gastroduodenal physiology that could lead to the development of peptic ulceration, and evidence suggests that some of these effects may be potentiated in *H. pylori*-positive persons. Taken together, these data strongly suggest a causal relationship between smoking and the development of peptic ulcers, at least in *H. pylori*-positive persons. There is insufficient evidence to evaluate the relation between smoking and peptic ulcers in those who are *H. pylori* negative. Conflicting and inadequate data link smoking to ulcer occurrence in NSAID users and it is not possible to evaluate an independent effect for smoking in the development of NSAID-induced peptic ulcers.

There is evidence to suggest that after adjusting for NSAID use, smoking may be associated with an increased risk of peptic ulcer complications, including perforation and bleeding. Data from the most recent study (Weil et al. 2000), however, suggest that this effect may be restricted to nonusers of NSAIDs.

The effects of smoking cessation on ulcer risk have not been evaluated in the context of *H. pylori* infection. However, the transient nature of many of the physiologic effects of smoking suggests that an excess risk may be restricted to current smokers.

Ulcer Healing and Recurrence

Healing and recurring *H. pylori*-positive ulcers are closely associated with eradication and recurrence of the infection. The evidence strongly suggests that if *H. pylori* is eradicated, smoking has no effect on either the healing or recurrence of ulcers. There is, however, evidence to suggest that *H. pylori* eradication therapy is somewhat less successful for current smokers. There are no good data to evaluate the effects of smoking on the recurrence of ulcers associated with *H. pylori* infection when long-term *H. pylori* eradication fails, or on the treatment and recurrence of ulcers in persons negative for *H. pylori* infection.

Conclusions

1. **The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are Helicobacter pylori positive.**
2. **The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are Helicobacter pylori negative.**
3. **The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of nonsteroidal anti-inflammatory drugs.**
4. **The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.**

Implications

The prevalence of *H. pylori* has declined in developed countries (Banatvala et al. 1993; Kosunen et al. 1997) and, as a result, the proportion of patients with *H. pylori*-negative ulcers will increase, making them an important group to study. Also, an increasing number of *H. pylori*-negative ulcers may not be attributable to NSAID use or other established causes of ulcers (Jyothiswaran et al. 1998). The rarity of ulcer recurrence when *H. pylori* is eradicated, regardless of smoking status, suggests that smoking is not an important factor in the initial development or recurrence of ulcers among persons who are *H. pylori* negative. However, this topic has not been well investigated, largely because of the paucity of such ulcers, and is likely to be an important area for future research.

Because the main effects of smoking on gastrointestinal physiology appear to be short-lived, it is likely that smoking cessation will both reduce ulcer occurrence in those persons who are *H. pylori* positive and improve the chances of eradication in patients (with or without ulcers) treated for *H. pylori* infection. Even if eradication is successful, it seems unlikely that a continuation of smoking will influence the course of peptic ulcer disease.

Table 6.33 Studies on *Helicobacter pylori* (*H. pylori*) eradication rates among smokers and nonsmokers

Study/location	Population	Therapy
Cutler and Schubert 1993 United States	98 patients with [illegible] gastric ulcers, duodenal ulcers, or nonulcer dyspepsia	Bismuth, tetracycline, and metronidazole
Labenz et al. 1994 Germany	405 patients with [illegible] duodenal ulcer [illegible] 651 [illegible] duodenal ulcer [illegible] 109 [illegible] gastric ulcer [illegible] with positive [illegible] status with [illegible] [illegible]	[illegible]
O'Connor et al. 1995 Ireland	83 patients with duodenal ulcer [illegible] [illegible] [illegible] [illegible]	Bismuth, tetracycline, and metronidazole
Bardhan and Salih 1997 United Kingdom	200 patients with endoscopically proven [illegible]	Bismuth, tetracycline, and [illegible] [illegible] [illegible] and metronidazole [illegible] [illegible] [illegible] and [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
Bardhan et al. 1997 Canada, Ireland, United Kingdom, United States	281 duodenal ulcer patients with *H. pylori* infection	[illegible] omeprazole
Brown et al. 1997 Korea	79 patients with [illegible] gastritis and [illegible] [illegible] [illegible] [illegible]	Amoxicillin, clarithromycin, and omeprazole
Breum et al. 1997 Korea	79 patients with [illegible] duodenal ulcer [illegible] [illegible] [illegible]	Metronidazole, amoxicillin, [illegible]
Kadayifci and Simsek 1997 Turkey	200 patients with endoscopically verified [illegible] duodenal ulcer disease	Omeprazole, clarithromycin, metronidazole, ranitidine, bismuth citrate, and tetracycline [illegible]

[illegible] = Data were not reported.
NS = Not significant.

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Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	Nonsmokers	
NR*	73.7	89.7	16.0 (p = 0.040)
NR	81	83	2 (p = 0.77)
NR	94.6	94.4	−0.3 (NS)
NR	ETT 69.3 OCMS 85.2 OCTS 68.2 OCBs 78.5	84.2 90.6 87.2 85.2	14.9 (NS) 5.4 (p = 0.05) 19.0 (NS) 6.7 (p = 0.05)
NR	71	77	6 (NS)
NR	95.7	100	4.3 (p = 0.06)
[illegible]	[illegible]	[illegible]	23 (p = 0.015)
Fecal ulcer risk were stratified by diagnosis, by cigarettes/day, by tobacco load (Brinkman Index), by the study's enrollment criteria, and by [illegible]	0–20 cigarettes/day 66 >20 cigarettes/day 59	68	2 (NS) 9 (NS)

Table 6.33 Continued

Study/location	Population	Therapy
Moayyedi et al. 1997 United Kingdom	275 *H. pylori*-positive patients, diagnosed by [illegible] UBT (127 with normal endoscopy, 98 with duodenal ulcers, 18 with gastric ulcers, and 24 with [illegible])	Omeprazole, clarithromycin, and tinidazole
[illegible] Japan	127 [illegible] with [illegible] gastric [illegible] disease	20 [illegible] clarithromycin

Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	Nonsmokers	
NR	87	95	8
[illegible]	[illegible]	81.0	22.5 (p = 0.01)

Conclusions

Diminished Health Status

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.
2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Loss of Bone Mass and the Risk of Fractures

3. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.
4. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.
5. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.
6. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.
7. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Dental Diseases

8. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.
9. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.
10. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Erectile Dysfunction

11. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Eye Diseases

12. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.
13. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.
14. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.
15. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.
16. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.
17. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.
18. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Peptic Ulcer Disease

19. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.
20. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

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21. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of nonsteroidal anti-inflammatory drugs.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

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